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HYPOGLYCEMIA

THE CLINICAL SYNDROME, ETIOLOGY AND TREATMENT: REPORT OF A CASE DUE TO HYPERINSULINISM *

GEORGE D. GAMMON, M.D.
Edward W. Bok Fellow in Medicine, University of Pennsylvania; Assistant Physician to Gastro-Intestinal Section of Medical Clinic, University Hospital
PHILADELPHIA
AND
WILLIAM C. TENERY, M.D.
Director, Waxahachie Sanitarium
WAXAHACHIE, TEXAS

The spontaneous appearance of hypoglycemia may result from certain abnormalities of any of the factors controlling carbohydrate metabolism. A survey of the literature indicates that the condition may arise in the most diverse clinical states. In the present article, we undertake a classification of the various types of hypoglycemia, citing illustrative examples of each. Since pancreatic hypoglycemia appears most frequently clinically, this form has been emphasized by a detailed review of the syndrome based on an analysis of the reported cases. A report is given of a patient suffering from hypoglycemia of pancreatic origin. Tables abstracting the details of the available reports on pancreatic hypoglycemia and of leading cases of the other types are included.

In order better to orient the discussion, we present a classification of the diseases in which hypoglycemia appears spontaneously. We wish this to be considered merely as a tentative etiologic framework, for an entirely adequate scheme will be possible only when the mechanisms of the underlying disturbances of carbohydrate metabolism in the various diseases are thoroughly understood.

TYPES OF SPONTANEOUS HYPOGLYCEMIA

Endocrine Hypoglycemia
Pancreatic
A. Hyperfunction or hyperinsulinism, diffuse hypertrophy and tumors of the islets: dysinsulinism or dysinsulinosis
B. Late diabetes

* Submitted for publication, Oct. 25, 1930.

C. Alimentary hypoglycemia
Suprarenal insufficiency
Pituitary dysfunction
Thyroid insufficiency
Pluriglandular syndromes

Other Types of Hypoglycemia
Hepatic
Muscular dystrophy
Renal diabetes
Lactation and pregnancy
Fatigue
Infections
Terminal hypoglycemia

ENDOCRINE HYPOGLYCEMIA

PANCREATIC HYPOGLYCEMIA: A. HYPERFUNCTION OF THE ISLETS

Hypoglycemic attacks have appeared spontaneously when the pancreas has shown increased island tissue in two forms, diffuse hypertrophy or circumscribed neoplasia, both malignant and benign; they have also appeared when there was no visible evidence of increased islet tissue. A brief history of the evidence permitting this statement follows.

History of the Concept of Hypoglycemia Due to Hyperfunction of the Islands of Langerhans.—Fischler [1] first described hypoglycemic shock under the title "glucoprivative intoxication"; this appeared in dogs with Eck fistulas rendered diabetic by phlorizin. Harris,[2] in 1924, surmised that a clinical condition of hyperfunction of the islands of Langerhans should produce the same symptoms observed after an overdosage of insulin. He reported five cases which he considered of this origin under the terms, "hyperinsulinism" and "dysinsulinism." No pathologic studies were made.

Evidence that diffuse hypertrophy of the islets could cause hypoglycemia was presented by Gray and Feemster [3] in 1926. A child born of a diabetic mother died of hypoglycemic shock. The enlargement of the islands in the child's pancreas was considered the result of an attempt to compensate for the hormone missing in the maternal circulation. Diffuse hypertrophy of island tissue occurs also after blockage of the pancreatic duct; de Takats, Hannett, Henderson and

1. Fischler, F.: Physiologie und Pathologie der Leber, Berlin, Julius Springer, 1916.

2. Harris, S.: Hyperinsulinism and Dysinsulinism, J. A. M. A. **83**:729 (Sept. 6) 1924.

3. Gray, S. H., and Feemster, L. C.: Compensatory Hypertrophy and Hyperplasia of the Islands of Langerhans in the Pancreas of a Child Born of a Diabetic Mother, Arch. Path. **1**:348 (March) 1926.

Seitz [4] presented evidence that this hypertrophy is accompanied by an increase in the function of the islets. Wilder [5] referred to Jaffé's patient who showed hypertrophy of the islands from blockage of the pancreatic duct by a scirrhous carcinoma of the pancreatic head; it is not known whether hypoglycemia developed in this case.

That hypoglycemia could result from a tumor of the islands of Langerhans was demonstrated convincingly in 1927 by Wilder, Allan, Power and Robertson's [6] patient. Extracts from the carcinoma and from metastases in the liver yielded insulin. Further proof of the relation of tumors of the islands and hypoglycemia was supplied in 1929 by Howland, Campbell, Maltby and Robinson; [7] the removal of a small carcinoma of the islets was followed by cessation of the hypoglycemic attacks. Benign tumors may also produce hypoglycemia; McClenahan and Norris [8] described the hypoglycemic death of a Negro whose pancreas contained an adenoma originating in the islands. Not all adenomas of the islands, however, are accompanied by hypoglycemia. Warren [9] collected twenty reports of adenomas of the islands of Langerhans in which none of the patients had suffered hypoglycemic shock during life.

Nor may one assume that all cases of pancreatic hypoglycemia are the result of diffuse hypertrophy or tumor of the islets. Hyperfunction of the islands may occur in a pancreas morphologically normal, as was first demonstrated by Finney and Finney.[10] It should be recalled that in the opposite condition of diabetes, changes in the islands are not always demonstrable, so that normal morphology does not prove normal function. It should be emphasized that altered function is of more importance than structural change.

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4. de Takats, G.; Hannett, F.; Henderson, D., and Seitz, I. J.: Correlations of Internal and External Pancreatic Secretion; Effect of Isolation of the Tail of the Pancreas on Carbohydrate Metabolism, Arch. Surg. **20**:866 (May) 1930.

5. Wilder, R. M.: Recently Discovered Endocrine Diseases, Hyperepinephrinism, Hyperinsulinism and Hyperparathyroidism, Internat. Clin. **1**:293 (March) 1930.

6. Wilder, R. M.; Allan, F. M.; Power, M. H., and Robertson, H. E.: Carcinoma of the Islands of the Pancreas, Hyperinsulinism and Hypoglycemia, J. A. M. A. **89**:348 (July 30) 1927.

7. Howland, G.; Campbell, W. R.; Maltby, E. J., and Robinson, W. L.: Dysinsulinism; Convulsions and Coma Due to Islet Cell Tumor of the Pancreas, with Operation and Cure, J. A. M. A. **93**:674 (Aug. 31) 1929.

8. McClenahan, W. U., and Norris, G. W.: Adenoma of the Islands of Langerhans with Associated Hypoglycemia, Am. J. M. Sc. **177**:93 (Jan.) 1929.

9. Warren, Shields: Adenomas of Islands of Langerhans, Am. J. Path. **2**: 335 (July) 1926.

10. Finney, J. M. T., and Finney, J. M. T., Jr.: Resection of the Pancreas, Ann. Surg. **88**:584 (Sept.) 1928.

The terminology of the literature recognizes this distinction: "Hyperinsulinism" implies an increased production of the hormone without stating the cause; "dysinsulinism" suggests a lack of normal control of the release of hormone. It is true that the terms have been used somewhat loosely and no clearcut distinction made. "Dysinsulinism" in the sense just mentioned might exist with a pancreatic tumor, and the term has been so employed by some writers,[7] or it might exist with a pancreas morphologically normal, as we have seen to be the case. It is precisely for the group of cases showing increased production and abnormal release of insulin in a morphologically normal pancreas that a specific term is needed. One might suggest "insulinosis" or "dysinsulinosis"; the actual term is immaterial, provided it is understood to characterize this group alone. If some such term is accepted, it would seem wise to use "hyperinsulinism" in a generic sense for overproduction of insulin, regardless of cause, and "dysinsulinism" generically for abnormal control of insulin production and release, whatever the etiology.

REPORT OF A CASE

The case to be discussed probably belongs to the group for which we have suggested the term "dysinsulinosis." The patient complained of symptoms typical of hypoglycemic shock; studies of her carbohydrate metabolism yielded results similar to those in the reported cases of pancreatic hypoglycemia, and she was completely relieved by the frequent ingestion of foods containing carbohydrate.

Miss A. C., an intelligent and cooperative unmarried woman, aged 39, came to Waxahachie Sanitarium in July, 1929, complaining of attacks of weakness and unconsciousness with muscular twitching.

The first symptom was a sudden lapse into unconsciousness in 1926. She had omitted supper the night before; when she arose in the morning and tried to walk, she fell; she talked irrationally, her lips trembled, and she was nauseated; then she became unconscious. In one hour she recovered, without treatment, and remembered nothing of the attack. A similar seizure occurred during each of the next three months; during the succeeding two years, she was entirely well.

In May, 1928, the attacks recurred, accompanied by slight convulsive movements of the hands and legs, but never of the jacksonian type. Once or twice diplopia warned of impending symptoms. Recovery was always spontaneous, and no recollection of the event remained. Five or six weekly attacks occurred at this time; in the intervals she was perfectly well.

She then discovered the value of food in aborting and relieving the attacks; in her unconscious states, however, she always resisted efforts to feed her. Rest at home on an augmented diet, but without additional feedings between meals, gave her entire relief.

One month after returning to secretarial work in the fall of 1928, the seizures recurred daily. By that time they had assumed two characteristic forms, a severe and a lighter attack. The lighter episodes consisted of irritability, weakness, perspiration, a tendency to mix words, and drowsiness succeeded by sleep unless food was taken. They appeared before the noon or evening meals. Cookies taken

between meals effectively warded off the attacks. The more severe attacks were the convulsive seizures described.

Various physicians told her that she was a victim of "nerves," information which considerably distressed this woman who had no neurotic tendencies. No change in weight had occurred during the illness; in 1926, she weighed 133 pounds (60.3 Kg.), and in 1930, 137 pounds (62.1 Kg.).

Then menses were established when she was 12 years of age; they occurred regularly at intervals of three weeks, and were normal in other respects. At the onset of hypoglycemia, they became irregular, being absent as long as three months. Subsequently, although the patient was still ill, they became regular.

No other medical history was elicited, except that she tended to be plump as a child. Measles and mumps were her only previous illnesses. None of the family had any symptoms suggesting hypoglycemia or diabetes. No family history of disease appeared relevant.

Physical examination revealed no abnormality. She was a well developed, somewhat rubicund, middle-aged white woman, who appeared in the best of health. The pupillary reactions were normal, as were the eyegrounds. The thyroid gland was rather prominent, symmetrical and soft; no bruit was heard; no stigmas of hyperthyroidism were present. The breasts were undeveloped. The lungs and heart were normal, except for a faint systolic bruit heard in the second interspace to the left of the sternum. The blood pressure was normal. Nothing abnormal

TABLE 1.—*Results of First Sugar Tolerance Test*

Time	Blood Sugar, Mg.	Urine Sugar
Fasting	50	0
45 minutes	225	0
60 minutes	230	0
120 minutes	225	0

could be felt in the abdomen. The liver was not enlarged. Neurologic examination for sensation, motor power, reflexes, cranial nerves and mentality gave negative results.

A diagnosis of hypoglycemic attacks was made because of the history of relief on the ingestion of food.

The blood counts were normal. The Wassermann reaction of the blood was negative. The blood sugar level was definitely low; on two occasions the fasting value was 45 and 52 mg., respectively.

The first test for sugar tolerance was made at a time when she was suffering daily hypoglycemic shocks. On July 6, 1929, 1.75 Gm. of dextrose per kilogram of body weight was administered, and the results given in table 1 were obtained on venous blood with the Folin-Wu technic.

The epinephrine test was performed: The blood sugar during fasting was 69 mg. The hypodermic administration of 0.6 cc. of epinephrine 1:1,000 was followed by a rise of blood sugar to 99 mg. in fifteen minutes and a fall to the fasting level in forty-five minutes. No undue reaction to the test was noted.

Results of the insulin test were: Ten units of insulin, administered while the patient was fasting, caused a drop in blood sugar of from 60 to 45 mg. in twenty minutes. There was a slight reaction, consisting of a vacuous, staring expression, slight tremor and perspiration.

Treatment.—When the diagnosis was established, the patient was placed on a diet with a high carbohydrate content, and feedings were given between the regular meals and at bedtime. She was immediately relieved: on this regimen there has been no recurrence in a year. She was able to return to work, and has apparently been perfectly well.

Since alimentary measures abolished the attacks completely, and since the long duration of her illness seemed evidence against a neoplastic lesion, observation was decided on rather than a partial pancreatectomy. During a year nothing appeared to alter this decision.

A second sugar tolerance curve taken nine months (April 12, 1930) after the first one gave the results shown in table 2.

The difference between the sugar tolerance curve made on admission when she was having a shock daily and that after nine months without symptoms on a diet with a high carbohydrate content is striking. Reference will be made to the possible cause in the discussion of the tolerance curves in the reported cases.

Symptoms of Spontaneous Hypoglycemia of Pancreatic Origin from an Analysis of the Reported Cases.—The symptoms of pancreatic hypoglycemia, appearing spontaneously at intervals, resemble those of insulin shock; the intervals tend to become shorter and the seizures more severe. Relief occurs spontaneously or after the ingestion of any food containing carbohydrate, except in severe terminal attacks. Commonly between the attacks, at least early in the disease, the patient is perfectly well.

TABLE 2.—*Results of Second Sugar Tolerance Test*

Time	Blood Sugar, Mg.	Urine Sugar
Fasting	47	0
45 minutes	145	0
1 hour, 45 minutes	125	0
2 hours, 45 minutes	111	0

The actual seizure may be described as follows: A sense of weakness and extreme fatigue assails the patient, usually after a short fast; if walking, he feels unable to proceed a step farther; a vague nervousness supervenes; the hands tremble; sweat breaks out on the body; an intense hunger proclaims the need for food. Disturbances in vision are frequent: diplopia, dimness and loss of acuity are most common. Vertigo and ataxia may follow, as may nausea, vomiting and epigastric pain. Often an appalling sense of imminent dissolution is experienced. The patient may cry out or sing. Mental confusion becomes apparent to the observer in incoherent speech, irritability and irrational action. Unconsciousness quickly follows, consisting of somnolence or deep stupor, which at times may be momentarily interrupted by questioning or by painful stimuli. The stupor may last for several hours or even for days. More frequently, however, unconsciousness is soon followed by convulsions. The spasms are of the clonic type, beginning in the face with grimacing movements and spreading to all the extremities simultaneously. The convulsions commonly are neither prolonged nor

severe. Breathing is said not to be stertorous, and cyanosis is absent; the latter observation probably depends solely on the duration of the convulsion. Foaming at the mouth is frequent; loss of sphincteric control is uncommon. Nystagmus, trismus and inability to swallow have been noted.

The convulsion is usually over in from a few minutes to a half hour, and even without food, the patient, dripping with sweat and saliva, becomes conscious. Recovery is complete, without memory of the accident; however, temporary hemiplegia and occasionally other minor neurologic residua, which clear up after several days, have been noted. Paresthesias of the tongue and lips, following or preceding the attack, have been described.

While in most cases the symptoms develop in the progression described, certain more fulminant attacks resemble completely an epileptic seizure. In other instances the episodes may be mild and innocuous.

Complete abortion of the attack in any stage is produced by the administration of carbohydrate. The only exception is in certain terminal cases. It should be noted that in some persons even the sight of food seems to precipitate symptoms; in our case, during an attack brought on by insulin, the patient seemed distinctly worse for a few moments after eating candy, and then rapidly improved. These observations suggest that there is either an overproduction of insulin in response to a normal stimulus, or an insufficient release of glycogen from storage depots to prevent hypoglycemia.

Recurrence of attacks with increasing frequency is characteristic of pancreatic hypoglycemia. The early seizures are usually separated by considerable time, from two years to several weeks, but over the course of several years or months they become more frequent until the incidence is one or more a day. With the increasing frequency there is a tendency for the attack to become more severe.

Sex and Age Incidence.—About twice as many cases have been reported in males as in females. Menstrual irregularity and an increase in the attacks during menstruation have been observed in a few of the women. The most frequent age incidence is from 31 to 50 years. The disease may, however, appear at any age.

Past History.—Previous transitory glycosuria, easily controlled by diet and tending to disappear, was present in about a fourth of the patients. One patient [10] was known to have had a high blood sugar content a year before hypoglycemia developed. This observation of a previous glycosuria is the most significant fact gleaned from a study of the past histories. While its relation to subsequent hypoglycemia is not clear, it certainly leads to the hypothesis that the previous elevation of blood sugar eventuated in a hyperfunction of the islets, which

TABLE 3.—*Symptoms of the Attack*

Cases	Early				Later							
	Nervousness	Weakness Fatigue	Gastro-Intestinal Symptoms	Neuromuscular Symptoms	Disturbances of Mental State	Neuromuscular Symptoms	Onset	Repeated Attacks	Frequency	Relieved by	Symptoms During Interval
Pancreatic											
1. Harris[2] (case 1).....	+	+ (C.C.)	Hunger	.....	.....	.....	1 hour before meals	+	Daily attacks	Food	
2. Harris (case 2).....	+	+	Hunger (C.C.)	Tremor; sweating	Sense of dying	.....	1 hour before meals	+	Daily attacks	Food	Weakness
3. Harris (case 3).....	+ (C.C.)*	+ (C.C.)	Hunger	Tremor	.....	.....	Before meals	+	.....	Food	
4. Harris (case 4).....	+	+ (C.C.)	.....	.....	.....	.....	Before meals	+	.....	Food	
5. Harris (case 5).....	+	+	Hunger	.....	.....	.....	Before meals	+	.....	Food	
6. Laroche and Bussière (Rev. méd.-chir. d. mal. du foie **3**: 481 [Nov.-Dec.] 1928)	—	—	Occasional vomiting and dysphagia	Tremor; diplopia; vertigo, trismus	Crying; singing; unconsciousness (once for 3 days)	Occasional convulsion; loss of urinary sphincter control	On rising	+	3 months later became progressively more frequent and severe	Food	Weakness; mental impairment
7. Sendrail and Planques (Gaz. d. hôp. **100**: 1105 [Aug. 20] 1927; 1137 [Aug. 27] 1927)	—	+ (C.C.)	Nausea; abdominal cramps	.....	Confusion; impairment of speech	.....	1 hour before noon meal	+	.....	Food	Asthenia
8. Hartmann (M. Clin. North America **12**: 1035 [Jan.] 1929)	—	+	.....	Diplopia	Semiconsciousness	Convulsions; began in face	Before meals	+	Increasing frequency and severity	Food	Well early; gradually grew weaker
9. Zubirán (Medicina, Mexico **9**: 306 [April] 1929)	+	+	Hunger (C.C.)	Tremor; vertigo; sweating	Unconsciousness	Convulsions	Before meals	+	Increased in 1 year from occasional to daily	Food	Well; gained weight
10. Finney and Finney[10].....	+	+	.....	Tremor; squint; diplopia; vertigo	Crying; singing; confusion; semiconsciousness	Convulsive movements of head	On rising	+	Initially 6-8 months; increased in 2½ years to daily	Food	Weakness
11. Allan (case 2) (Arch. Int. Med. **44**: 65 [July] 1929)	—	+ (C.C.)	.....	.....	Unconsciousness; (C.C.); stuporous 1 week once	Convulsions	Fasting or exertion	+	Occasional; increased in 3 years to 3 or 4 per week	Food	Weakness

* C.C., chief complaint.

12. Allan (case 3)	—	+	.....	.....	Mania once; unconsciousness	Convulsions	Fasting or exertion	+	Occasional; increased in 3 years to 3 or 4 per week	Food	Weakness
13. Gammon and Tenery	+	+	Vomiting	Tremor; diplopia; sweating	Crying; stupor	Convulsions; began in face	Before meals	+	2 years; increased in year to daily	Food	Well
14. Nielson and Eggleston (J. A. M. A. 94 : 860 [March 22] 1930)	—	—	.....	.....	Crying; unconsciousness	"Petit mal"; "grand mal"	.....	+	6 months to daily	Food	Well
15. Nielson and Eggleston (case 2)	—	—	.....	.....	Crying; unconsciousness	"Petit mal"; "grand mal"	.....	+	2 or 3 weeks	Food	Well
16. Nielson and Eggleston (case 3) (also Winans: South M. J. 23 : 402 [May] 1930)	—	—	.....	.....	Crying; automatonism	"Petit mal"; "grand mal"	On rising	+	.....	Food	Well
Tumors of Pancreatic Islands											
17. Wilder, Power, Allan and Robertson[8]	+	+ (C.C.)	Hunger	Tremor; vertigo; diplopia; sweating	Unconsciousness	Convulsions	Fasting	+	One per year; in next year increased to every 3 hours	Food; later required dextrose by vein	Weakness
18. Thalhimer and Murphy[11]	+	+	.....	Sweating	Unconsciousness	Convulsions began 1 year after onset	During morning	+	2 wk. to 2 mo.; during 2 yr. increased to 3 per day	No evident relation to food	Weakness
19. Howland, Campbell, Maltby Robinson[2]	—	+	Vomiting	Diplopia; sweating	Unconsciousness	Convulsions; began with facial grimacing	Fasting	+	3 months; in 7 years increased to 1½ hours	Food	Hemiparesis twice; recovered
20. McClenahan and Norris [5]	—	+	Hunger	.....	Confusion; difficulty of speech; unconsciousness	Convulsions	Fasting	+	Increased to daily in 6 months	Food; later dextrose by vein ineffective	Asthenia; loss of memory (C.C.)
Pituitary											
21. Wilder[27] (case 1)	.....	+	Vomiting	Diplopia; tremor; paresthesia of face and tongue	Difficulty of speech; hypomania, unconscious ½ to 38 hours	Loss of urinary sphincter control	Before meals	+	1 year; increased to several daily	Food	Headaches
22. Wilder (case 2)	.....	+	Hunger	Tremor; diplopia; vertigo; sweating	Crying; singing semiconsciousness	Convulsions involving face and arms; loss of urinary sphincter control	On rising	+	1 month; increased to daily	Food	Memory, vision, hearing impaired

TABLE 3.—*Symptoms of the Attack—Continued*

Cases	Early				Later							
	Nervousness	Weakness Fatigue	Gastro-Intestinal Symptoms	Neuromuscular Symptoms	Disturbances of Mental State	Neuromuscular Symptoms	Onset	Repeated Attacks	Frequency	Relieved by	Symptoms During Interval
Pluriglandular											
23. Stenström[13]	—	—	.....	.....	Attack of coma	Rigidity of entire body	.....	—	One attack	Dextrose and epinephrine	
24. Petterson[35]	—	+	.....	.....	Unconsciousness	Convulsions	With diarrhea and fever	+	Occurred with diarrhea and fever	Food	Headache
25. Longcope[22]	—	—	.....	Vertigo	Excitation; unconsciousness	.....	Fasting	+	Several a year	Food	Scleroderma
Hepatic											
26. Nadler and Wolfer[37]	—	+	.....	.....	Unconsciousness	Convulsions involving face and arms	Fasting	+	1 to 7 times a day; increasing frequency	Dextrose	Carcinomatous cachexia
27. Griffiths[39] (case 1)	—	—	Vomiting; (C.C.) dysphagia	Strabismus	Crying; unconsciousness	Convulsions (C.C.)	After vomiting	+	1 to 4 times a year	Dextrose	Well
28. Snapper and Van Creveld[40]	No symptoms										
29. Wagner and Parnass[41]	No symptoms										
Renal											
30. Gibson and Larimer[45]	+	+	.....	Tremor; sweating	.....	.....	Fasting	+	Very infrequent	Food	Well
Lactation											
31. Stenström[49]	+	+	Hunger	Tremor; sweating	Unconsciousness	Convulsions	Fasting	+	1 week	Food; weaning child	Well

terminated in hypoglycemic attacks. Occasional glycosuria was noted in three patients at the time of examination. A lowered renal threshold after tests for sugar tolerance was noted once.

A history of gastro-intestinal disturbances appears fairly frequently: flatulence, epigastric burning and constipation. Two patients were operated on for undiscovered peptic ulcers. One had gallstones. Syphilis apparently plays no etiologic rôle. Other reported illnesses appear unrelated etiologically. In two instances a member of the family was similarly affected.

Physical Examination.—Physical examinations yielded no significant findings. There is no constant tendency to be over or under weight. The occasional observation of peripheral neuritis, a palpable liver, a hairless chest and sparse pubic hair, a nodular thyroid without other signs, and poor general development appeared to be merely coincidental. In one patient with pancreatic carcinoma and hepatic metastasis, the liver was palpable.

Laboratory Investigation.—The degree of lowering of blood sugar bears no quantitative relation to the symptoms. Estimations made during fasting range from 60 mg. to "too low to be read."[11] During the attack the average was 43 mg., with extremes of from 95 to 20 mg.

Sugar tolerance curves in seven of nine patients tested reached an abnormal height after the ingestion of dextrose and remained elevated over two hours. The result is comparable to that seen occasionally in normal persons on a low carbohydrate intake. It is possible that repeated insulin shocks deplete the glycogen stores of these patients, thus causing abnormal tolerance curves similar to those obtained after a restricted carbohydrate intake. The slight response of the blood sugar to injections of epinephrine might be regarded as supporting this view. In our case the first test of tolerance showed an abnormal rise and a delayed fall; the second curve made after a high intake of carbohydrate and freedom from shock for nine months was normal. At the later test the glycogen storage may have been more adequate.

To obtain an estimate of glycogen storage, the response of the blood sugar to the injection of epinephrine was observed. No characteristic effect appeared, but in general there was a tendency for the curves to be somewhat low. Such results suggest either diminished glycogen deposits or a faulty mechanism of release. One may not, however, interpret these observations in a strictly quantitative sense.[12] Ephedrine is credited with a slight effect in raising the blood sugar in two cases.

11. Thalhimer, W., and Murphy, F. D.: Carcinoma of the Islands of the Pancreas; Hyperinsulinism and Hypoglycemia, J. A. M. A. **91**:89 (July 14) 1928.

12. Brill, S.: Glycogenolysis Due to Epinephrine in Hepatic Disease, Arch. Surg. **18**:1803 (April) 1929.

TABLE 4.—*Sex, Age, Duration of Symptoms, Past History and Physical Observations*

Case	Sex	Age at Onset	Duration of Symptoms	Total Duration After Onset		Glycosuria	Past Medical History	Positive Physical Observations	Weight Above or Below Standard
				Life	Death				
Pancreatic:									
1	M	62 yrs.	—	—	—	—	Epigastric distress; cystitis		—
2	M	52 yrs.	—	—	—	+ 1 time	History of syphilis; negative Wassermann reaction of blood; previous constipation; bronchitis	Pulse rate 40	—
3	F	39 yrs.	—	—	—	+	Gaseousness; healed abscess of lung	Slight exophthalmos, tremor	+
4	F	27 yrs.	2 yrs.	—	—	0	Chronic appendicitis; tonsillitis		—
5	M	57 yrs.	2 yrs.	—	—	0	Gallstones; pain relieved by food; previous meningitis; injured spine in fall; bronchitis		
6	F	31 yrs.	4 yrs.	4 yrs.	4 yrs.	—	Visceroptosis; "coelialgia"; attack of polyneuritis	Polyneuritis	+
7	M	57 yrs.	5 yrs.	5 yrs.	—	—	Cramps; nausea		—
8	M	39 yrs.	4 yrs.	—	7 yrs.	0	Wassermann reaction of blood positive; epigastric distress; sour eructations	No hair on chest; pubic hair sparse; liver edge palpable	0
9	M	46 yrs.	5 yrs.	—	—	+ 4 yrs. before onset; 0 at onset			+
10	F	49 yrs.	4 yrs.	4 yrs.	—	0	Chronic indigestion and constipation; marked nervous instability; two breakdowns; dysmenorrhea; no pregnancies	Nodular thyroid	+
11	M	49 yrs.	3 yrs.	3 yrs.	—	0			..
12	M	43 yrs.	4 yrs.	4 yrs.	—	0			..
13	F	36 yrs.	3 yrs.	3 yrs.	—	0	Irregular menses at onset of hypoglycemia		+
14	F	24 yrs.	3 yrs.	2 yrs.	—	0			0
15	M	25 yrs.	5 wks.	3 mos.	—	0			0
16	M	10 yrs.	13 yrs.	18 mos.	—	0			..

Tumors of Pancreatic Islands:									
17	M	38 yrs.	18 mos.	—	19 mos.	+, traces for 3 yrs.	Operated for ulcer at 32 years; none found; renal stone at 37	Negative; paternal cousin died with similar symptoms	—
18	F	54 yrs.	2½ yrs.	—	2½ yrs.	0	Uterine fibroid	Poorly developed	—
19	F	42 yrs.	7 yrs.	7 yrs.	—	0	Cystitis at 32	Slight loss of weight	—
20	M	41 yrs.	6 mos.	—	6 mos.	0	Loss of memory; died of bronchopneumonia		—
Pituitary:									
21	F	42 yrs.	3 yrs.	3 yrs.	—	0		Bilateral facial impairment of sensation for pain and touch	—
22	F	52 yrs.	3 yrs.	3 yrs.	—	0	Always nervous; hysterectomy at 36	Dermographism; acromegaloid type.	—
Pluriglandular:									
23	F	34 yrs.	1 yr.	1 yr.	—	0	Azotemic nephritis; no menses	No axillary or pubic hair; hair of the head and eyebrows scanty; positive Babinski sign bilaterally in coma	—
24	F	30 yrs.	5 mos.	—	3 mos.	0	Amenorrhea and loss of axillary and pubic hair after childbirth at 27	No axillary or pubic hair; secondary anemia; hypertonic muscles and hands in position of tetany during attack	—
25	M	39 yrs.	2 yrs.	2 yrs.	—	0		Scleroderma; bronze skin; hypotension	—
Hepatic:									
26	M	30 yrs.	1st attack	—	3½ mos.	0	Primary carcinoma of liver	Large nodular liver; cachexia	—
27	M	2 mos.	2 mos.-5 yrs.	5 yrs.	—	0	Convulsions at 4 months	Well developed	0
28	M	?	7 yrs.	7 yrs.	—	0		Undersized; very large liver	—
29	F	?	?	8 yrs.	—	+, alternated with ketonuria		Very large liver; saddlenose	—
Renal:									
30	F	40 yrs.	10 yrs.	10 yrs.	—	+			—
Lactation:									
31	F	40 yrs.	1 yr.	1 yr.	—	+	Aortic and mitral regurgitation; tuberculosis; glycosuria a few times; nursing a child	Ridigity during coma	—

TABLE 5.—*Laboratory Data*

Case	Blood Sugar, Mg. per 100 Cc.				Sugar Tolerance Curve	Urinary Sugar	Epinephrine Test	Pituitary Test	Insulin Test	Miscellaneous Observations
	Fasting	During Attack	Lowest	Symptom Level						
Pancreatic:										
1	65-70	—	65-70	65-70	High rise; returned to normal in 3¼ hours	.....	.....	.....	.....	
2	65	—	65	—	Normal	+ once	.....	.....	.....	
3	47-111	95-47	47	—	.....	Previously +; none when seen	.....	.....	.....	
4	56	—	56	—	.....	.....	.....	.....	.....	
5	67	—	67	—	.....	.....	.....	.....	.....	
6	75	66	66	—	Abnormally high; remained high 3 hours	.....	6 to 100 in ½ hour	Cured attack	No hypersensitivity	Fat caused attack; respiratory quotient rose to unity after dextrose; sella turcica normal; basal metabolic rate normal
7	—	62	62	—	.....	.....	No effect in attack	.....	.....	
8	—	25-42	42	—	216 at 2 hours	.....	Cured attack	Cured attack	.....	Disks pallid; moderate contraction of temporal fields; basal metabolic rate normal
9	70	58	58	58 (?)	Low rise	Previously +; glycosuria when blood sugar was 117 mg.	.....	.....	.....	
10	220 (1925) 134 41 (1926) 30 (1927)	20-30	20	—	74-232, 196 at 2 hours (1926) Normal (1927)	.....	Blood raised to normal	Raised blood sugar	10 units caused attack	Spinal fluid sugar 34 mg.; sella turcica normal; basal metabolic rate —9 per cent
11	60	60-40	40	60	.....	.....	Slight rise in blood sugar; cured attack	Cured attack	.....	
12	..	50-40	40	50	.....	.....	Slight transitory rise in blood sugar	Slight transitory rise in blood sugar	.....	Ephedrine cured symptoms
13	45-52	45	45	—	Diabetic type (1929) Normal (1930)	+	69 to 99 in 15 min.	.....	10 units caused attack	
14	85-101	—	50	—	Low rise; previous curve reported of diabetic type	.....	.....	.....	.....	Basal metabolic rate normal
15	34-90	—	34	Below 34	Low rise; 34 at 2 hours	.....	.....	.....	.....	
16	93	—	64	—	Normal	.....	.....	.....	.....	
Tumors of Pancreatic Islands:										
17	68	55-27	27	55	Remained high at 2 hrs., 31 at 3 hrs.	+; traces for 3 years	No rise in blood sugar	No rise in blood sugar	.....	Fat caused attack in 30 min.; respiratory quotient 0.9; went to 1.06 after dextrose; liver weighed 3,300 Gm.; 8.25% glycogen; metastatic tumor contained insulin; basal metabolic rate +27%; rose to +43% after dextrose

18	"Too low to read" 60	"Too low to read" 60	60	"Too low to read"	.....	.....	.....	.....	.....	Spinal fluid contained 30 cells; Wassermann reaction negative
19	80	40	40	—	80 (fasting) to 266; 240 at 3 hrs.; postoperatively normal, except 150 at 3 hrs.	.....	40 to 110 in 1 hr.	Caused rise in blood sugar	.....	Respiratory quotient 0.83-0.85; ephredrine caused slow rise in blood sugar; dihydroxy-acetone, 100 Gm., cured shock; tumor contained insulin; sella turcica normal; basal metabolic rate —96 % of normal
20	—	38-42	38	—	.....	.....	.....	.....	.....	Spinal fluid sugar 20 mg. during shock
Pituitary:										
21	20	20	20	—	.....	.....	No effect on attack	.....	.....	Sella turcica slightly large
22	60	50-90	50	—	Hypoglycemia at 4 hrs.	.....	Cured attack	No effect	.....	Sella turcica slightly large
Pluriglandular:										
23	40-80	35	35	—	Normal	.....	Cured attack	.....	.....	Basal metabolic rate —30% (Krogh)
24	40-50	25	20	—	Low (40-80)	.....	63 to 87 in 1 hr.	.....	.....	Plasma carbon dioxide 39% by volume in attack; 60% when improved; 5 cc. of blood injected in rabbit did not lower blood sugar; sella turcica normal; basal metabolic rate —20% (Krogh)
25	52	47	47	51	Remained high; 143 at 2 hrs.	.....	.....	.....	.....	Basal metabolic rate —23%
Hepatic:										
26	25-70	—	25	—	158 at 3 hrs., 8/14 165 at 2 hrs.; 08 at 3 hrs., 9/1 100 at 2 hrs.; 62 at 3 hrs., 9/4	.....	No rise in blood sugar	No rise in blood sugar	.....	Van den Bergh normal; bromsulphalein excretion normal; blood cholesterol 176 mg.; 50 cc. of blood contained no insulin; terminal blood sugar 13 mg.; sella turcica normal; basal metabolic rate —9%
27	78-84	98	98	—	Normal except rise slight	.....	.....	.....	.....	.....
28	30-46	—	30	—	Normal except biphasic type	.....	Very slight rise in blood sugar caused vomiting	.....	10 units caused shock	Ketonuria and hypoglycemia on fasting; sella turcica normal; basal metabolic rate "slightly elevated"
29	"0"	—	"0"	—	See miscellaneous observations	+	No effect	.....	.....	Hyperglycemia and glycosuria alternated with ketonuria and hypoglycemia on fasting; sella turcica normal
Renal:										
30	58-91	58	58	62	See miscellaneous observations	+; renal diabetes	.....	.....	.....	Double administration of dextrose at 3 hour intervals caused shock in 4 hrs.
Lactation:										
31	40-50	—	40	—	.....	.....	.....	.....	.....	Fat caused attack

TABLE 6.—*Outcome of Cases*

Case	Etiology	Treatment	Result
Pancreatic			
1	Hyperinsulinism	Dietary	Cure (1 year)
2	Hyperinsulinism	Food third hour	Cure
3	Hyperinsulinism	Dietary	Cure
4	Hyperinsulinism	Dietary	Cure
5	Hyperinsulinism	Dietary	Cure
6	Hyperinsulinism; no postmortem examination	Dietary	Relief; died in attack without adequate treatment, 4 years after onset
7	Hyperinsulinism	Dietary	Cure
8	Hyperinsulinism; no postmortem examination	Food and sugar	Relief; died 7 years after onset
9	Hyperinsulinism	Dietary	Improved
10	Hyperinsulinism; pancreas normal	Resection of two-thirds of pancreas	Improved
11	Hyperinsulinism; pancreas normal	Food nine times per 24 hours; three times at night; resection of two-thirds of pancreas	Improved temporarily; returned to preoperative condition
12	Hyperinsulinism; pancreas normal	400-500 Gm. of carbohydrate per day; resection of two thirds of pancreas (Allan, Boeck and Judd: J. A. M. A. 94 : 1116 [April 12] 1930)	Unimproved
13	Hyperinsulinism	Dietary	Cure (9 months)
14	Hyperinsulinism	Dietary; suprarenal extract	Cure
15	Hyperinsulinism	Dietary; suprarenal extract	Cure
16	Hyperinsulinism	Dietary; suprarenal extract	Cure
Tumors of Pancreatic Islands			
17	Carcinoma of islands of Langerhans with liver metastasis; tumors contained insulin	20-25 Gm. of dextrose per hour by vein required; laparotomy	Died; not in hypoglycemia at time
18	Carcinoma of islands of Langerhans; pituitary gland normal	Food	Death in coma
19	Carcinoma of islands of Langerhans	Removal of tumor; 300 Gm. of dextrose per day and high diet required preoperatively	Cure (14 weeks)
20	Adenoma of islands of Langerhans; round cell infiltration of meninges	Dextrose	Death in coma
Pituitary			
21	Pituitary dysfunction	Food; roentgenogram of skull; thyroxin, 1 mg. by vein checked attack	Improved
22	Pituitary dysfunction	Food; roentgen therapy of skull; pituitary extract	Improved
Pluriglandular			
23	Pluriglandular	Thyroid and suprarenal extracts	Cured; blood sugar normal
24	Pluriglandular; small thyroid and pituitary glands; sclerosed suprarenal cortex and ovaries; pancreas normal	Dextrose cured attack	Died; not in shock; blood sugar 100 mg.
25	Pluriglandular	Thyroid extract	Scleroderma improved; hypoglycemia unimproved
Hepatic			
26	Primary carcinoma of the liver, 70-80% involved; metastasis to chest; liver deficient in glycogen; pancreas normal	Dextrose	Relieved attack; death from carcinoma
27	Hepatic (?); cyclic vomiting	Food and dextrose	Relief at time
28	Hepatic (?)	None	No change
29	Hepatic (?)	None	No change
Renal			
30	Renal diabetes	None	No change
Lactation			
31	Lactation	Weaned child	Cured

No observations of blood sugar after the administration of solution of pituitary appear to have been made; that elevation occurred, however, may be inferred from the fact that, in general, pituitary was effective in relieving shock.

No unusual sensitivity to insulin was noted in the three cases in which it was tested: two showed a slight reaction and one did not.

The sugar content of the spinal fluid was low in two instances during the attacks; 20 and 34 mg., respectively. No estimations of pressure were made on the spinal fluid.

A rise in the respiratory quotient to unity after the administration of dextrose in two of three patients has been adduced as evidence of unimpaired ability to utilize sugar. The basal metabolic rate was normal in four persons and plus 21 per cent in a fifth. The sella turcica was of normal size in five patients in whom roentgenograms were made.

Gastro-intestinal roentgenologic studies and tests of gastric secretion disclosed no striking abnormalities. No observations of peristalsis were made during an attack; in view of the increase of peristalsis after the injection of insulin, and the hunger and epigastric upset experienced by patients during shock, such studies might prove of interest.

Differentiation Between Cases of Hypoglycemia Due to Tumor and Those in Which the Pancreas Seems Morphologically Normal.—From an analysis of the case reports no reliable sign or symptom appears on which to base a diagnosis of tumor of the islands as opposed to their hyperfunction in the absence of neoplasia. This may be due in part to the relatively small number of case reports. Howland and his colleagues [7] were impressed by the erratic behavior in their case of tumor, "as if there were no nervous control" of the production of insulin. In Thalhimer and Murphy's case the attacks showed no relation to food. In the two groups no difference in age incidence was noted. The severity of the seizures was probably somewhat greater in the cases of tumor, though not invariably; asthenia between attacks was also somewhat more marked. The duration of symptoms when the patient was first seen was slightly less for the tumors, averaging 2.5 years with extremes of from 6 months to 7 years as against the average of 4 years for the nontumor group, with extremes of from 1 month to 13 years. Physical examination was of no value in the differentiation except in one patient in whom there was obvious metastasis to the liver. In no instance was the pancreatic tumor palpable. The death rate was of course higher for the tumor group; death occurred, on an average, 15 months after the onset of symptoms with extremes of from 6 months to 2.5 years.

In general, all that may be said is: There is perhaps a tendency for the disease to be more rapid in its development, more severe in

its manifestations, more erratic in behavior and more likely to cause death when tumor is present than in functional hypertrophy of the islands. No differentiation between adenoma and carcinoma seems possible, unless there is evidence of metastasis. There are insufficient reports of hypoglycemia from diffuse hypertrophy of the islands to attempt a differentiation from the other types.

TREATMENT AND RESULTS

The Attack.—Relief from the attack is usually easily accomplished by the administration of carbohydrates. In certain severe cases the intravenous injection of large amounts of dextrose is required. Drugs elevating the blood sugar level have proved effective. Epinephrine aborted the seizure in most instances, though it failed in a few; it proved more reliable than any other drug. Solution of pituitary achieves the same result, though less frequently; its action is slower and less marked than that of epinephrine. Ephedrine is still less effective. Suprarenal extract by mouth has recently been recommended. It was previously used with some success in pluriglandular cases,[13] but as yet the evidence is insufficient to judge its value in hyperinsulinism.

Interval Treatment.—Frequent feeding is the mainstay in preventing attacks of hypoglycemia. The diet should be high in carbohydrate. Fat should be used cautiously since it initiated attacks in three patients. In twelve typical cases of hyperinsulinism without proved tumor, in which dietary treatment was given, relief is reported to have occurred in ten; death in two. The intravenous injection of dextrose did not prevent the death of one patient suffering from adenoma. It seems likely that alimentary treatment has no influence on the basic disease process, merely providing enough carbohydrate to prevent shock. If more carbohydrate can be got into the body than the insulin metabolizes, it will be stored and prevent attacks; if more insulin is produced than can be "covered" by carbohydrate in the diet, the treatment will fail.

Roentgen therapy appears not to have been tried except in one case of carcinoma in which it was ineffective.

Surgical Treatment.—Partial pancreatectomy was first performed by Finney and Finney[10] in 1928. Allan, Boeck and Judd[14] recently reviewed the subject. Five patients without tumor formation in the pancreas have been so treated: three of these obtained slight improve-

13. Stenström, T.: Spontaneous Hypoglycemic Coma, Deutsches Arch. f. klin. Med. **152**:173 (Aug.) 1926.

14. Allan, F. N.; Boeck, W. C., and Judd, E. S.: Surgical Treatment of Hyperinsulinism, J. A. M. A. **94**:1116 (April 12) 1930.

ment but tended to relapse, and two obtained no relief. Resection of a small carcinoma of the islets [7] is the only instance on record in which operation on the pancreas resulted in complete cure. Two patients with carcinoma of the islets and metastasis to the liver who underwent laparotomy died from one to three months postoperatively. Thus the results of partial pancreatectomy have not, as yet, been satisfactory. In view of this fact, dietary management should first be tried unless neoplasm is suspected. If a dietary regimen fails, one may resort to partial pancreatectomy.

With this review of hyperfunction of the islands we wish to consider two other types of hypoglycemia of pancreatic origin, that of late diabetes and so-called alimentary hypoglycemia.

B. HYPOGLYCEMIA OF LATE DIABETES

A terminal hypoglycemia in diabetic patients untreated with insulin and not responding to dextrose has been observed many times. Jonas [15] reviewed several such cases and added one of his own, in which the patient died in hypoglycemic coma ten days after the suspension of insulin therapy. Joslin [16] also dealt with the subject.

C. ALIMENTARY HYPOGLYCEMIA

The secondary fall in blood sugar after the ingestion of food has occasionally been sufficiently marked to cause slight symptoms of hypoglycemia. This, however, is exceptional. The degree of fall of the blood sugar after the administration of dextrose has been proposed as a test of islet function.[17]

OTHER ENDOCRINE TYPES OF HYPOGLYCEMIA

After this somewhat detailed discussion of pancreatic hypoglycemia, based on a thorough review of the literature, we wish to characterize other types of hypoglycemia. For this purpose a summary of a few leading cases will be utilized; no attempt at an exhaustive review of the literature has been made for the nonpancreatic types. They are not always cleancut in etiology. Their symptoms are those of hypoglycemic shock, but they do not appear in the crescendo of severity and frequency characteristic of the pancreatic type.

Insufficient physiologic knowledge of the relations of various endocrine glands to carbohydrate metabolism makes attempts to evaluate

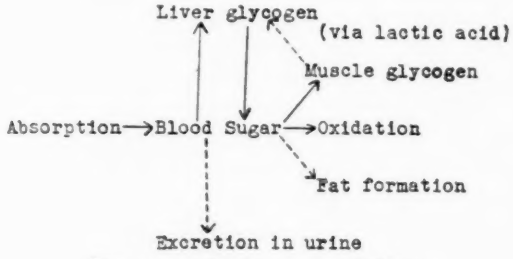
15. Jonas, L.: Hypoglycemia, M. Clin. North America **8**:949 (Nov.) 1924.

16. Joslin, E. P.: The Treatment of Diabetes Mellitus, ed. 4, Philadelphia, Lea & Febiger, 1928.

17. Depisch, F., and Hasenöhrl, R.: Beitrag zur Blutzucker-Regulation, Klin. Wchnschr. **5**:2011 (Oct. 22) 1926.

disturbances in these mechanisms clinically somewhat difficult. A carbohydrate cycle has recently been postulated by Cori and Cori [18] (chart). Their hypothesis states: "In the muscle the end product of glycogen breakdown is lactic acid; in the liver it is glucose. . . . The most probable point of attack of epinephrin is on the glycogenolytic process." Under its action "blood sugar derived from liver glycogen is utilized in the muscles, while lactic acid derived from muscle glycogen is carried back to the liver to replenish the glycogen that was lost, the end result being an increase in liver glycogen." [19]

Somewhat earlier Cannon,[20] writing on the sympathetic and suprarenal mechanisms for mobilizing sugar in hypoglycemia, divided the effect of hypoglycemia into two stages. The first stage, in which pallor, a rapid pulse rate, dilatation of the pupils and profuse sweating occurred, was the result of sympathetic stimulation. This sympathetic stimulation had the effect of liberating glycogen from the liver and liberating



Factors entering into a sugar balance.

epinephrine which, in turn, freed more liver glycogen and raised the level of the blood sugar. The effectiveness of this defense depended on the amount of liver glycogen and the amount of epinephrine present: if the suprarenal content was low, the first defense was weakened. The second stage was the convulsion which liberated more epinephrine and, through liver glycogen, raised the blood sugar level. In view of Cori and Cori's work, one might suppose that the lactic acid formed from muscle glycogen during the convulsion, through resynthesis to glycogen

18. Cori, C. F.: The Influence of Insulin and Epinephrine on the Fate of Sugar in the Animal Body, Harvey Lectures, Baltimore, Williams & Wilkins, 1927-1928, series 23, pp. 76-114.

19. A discussion of this work is given in Macleod, J. J. R.: Lectures on Physiology of Glycogen and the Rôle of Insulin and Epinephrine in Carbohydrate Metabolism, Lancet **2**:107 (July) 1929.

20. Cannon, W. B.; McIver, M. A., and Bliss, S. W.: Studies on Conditions of Activity in Endocrine Glands: Sympathetic and Adrenal Mechanism for Mobilizing Sugar in Hypoglycemia, Am. J. Physiol. **69**:46 (June) 1924.

in the liver, could be a further source of blood sugar. Clinically the blood sugar level rises after certain types of convulsion.[21] These observations, however incomplete, bear on three of the clinical states that we are about to consider: suprarenal insufficiency, hepatic destruction and muscular dystrophy.

SUPRARENAL INSUFFICIENCY

Various writers have attributed the weakness in Addison's disease to lowered blood sugar. Longcope,[22] in reviewing the literature, found hypoglycemia frequently present to a marked degree, though by no means universal. The blood sugar tends to remain at a low level without hypoglycemic attacks; though no observations of blood sugar are available, one wonders whether the cases of suprarenal insufficiency with convulsions and epilepsy are due to hypoglycemia. It is possible that the lowered synthesis of epinephrine fails to liberate glycogen from the storage depots.[23]

PITUITARY DYSFUNCTION

There remains considerable complexity in the relation of the pituitary body and its diseases to carbohydrate metabolism. Two observations seem authentic: The posterior lobe of the pituitary body is antagonistic to the action of insulin,[24] and diminution of posterior lobe secretion either experimentally or clinically results in a high tolerance for sugars.[25] Clinically, the syndrome supposed to result from insufficiency of the anterior lobe is accompanied by a high tolerance for carbohydrates.[26] Wilder[27] recently reviewed the relations of the hypophysis to sugar metabolism. He described a new syndrome, pituitary hypoglycemia, and reported two cases as examples of the condition. Both patients

21. Titus, P.; Willetts, E. W., and Lightbody, H. D.: Fluctuations in Blood Sugar During Eclampsia: Report of Additional Cases, Am. J. Obst. & Gynec. **19**:16 (Jan.) 1930.

22. Longcope, W. T.: Hypoglycemia in Scleroderma; Metabolism in Eight Cases with Reference to Function of Glands of Internal Secretion, J. A. M. A. **90**:1 (Jan. 7) 1928. See also Wadi, W.: Ueber Hypoglykämie bei Morbus addisonii, Klin. Wchnschr. **7**:2107 (Oct. 28) 1928.

23. Anderson recently described a case of tumor of the suprarenal with fatal hypoglycemia (A Tumor of the Adrenal Gland with Fatal Hypoglycemia, Am. J. M. Sc. **180**:71 [July] 1930).

24. Burn, J. H.: The Modification of the Action of Insulin by Pituitary Extract and Other Substances, J. Physiol. **57**:318, 1923.

25. Cushing, Harvey W.: The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott & Company, 1912.

26. Cushing, H.: Neurohypophysial Mechanisms from a Clinical Standpoint, Lancet **2**:175 (July 26) 1930.

27. Wilder, J.: Ein neues hypophysäres Krankheitsbild: Die hypophysäre Spontanhypoglykämie, Deutsche Ztschr. f. Nervenh. **112**:192 (May) 1930.

had slight enlargement of the sella turcica; one displayed slight acromegalic tendencies. The clinical course resembled that of mild hyperinsulinsim in the recurring seizures of hypoglycemia. An extract of the anterior lobe of the pituitary was of value in checking attacks.

In Wilder's [27] review, several persons with pituitary tumor are mentioned who showed hypoglycemia. Lloyd [28] found that a patient with proved pituitary tumor who died in convulsions also had hypertrophy of the islands of Langerhans and the parathyroids. Unfortunately, no estimations of blood sugar were made during the seizures.

THYROID INSUFFICIENCY

The evidence as to the existence and degree of hypoglycemia in hypothyroidism is controversial. Experiments indicate a lowered level for blood sugar following removal of the thyroid, at least in some animals.[29] It is also stated that increased tolerance for sugar occurs in myxedema,[30] so that large amounts of sugar may be taken without producing glycosuria. Campbell [31] found definite hypoglycemia and increased tolerance for carbohydrates in two cases of myxedema and in three cases of hypothyroidism following operation for exophthalmos. Administration of thyroid extract raised the fasting sugar level.

On the other hand, in hypothyroidism, cretinism and myxedema, Gray [32] observed normal values for sugar during fasting; sugar tolerance curves were high and sustained and were only slightly lower than those of persons with hyperthyroidism. Similar results are reported by Gardiner-Hill, Brett and Smith; [33] in fifteen myxedematous persons, the blood sugar value during fasting was about normal, while sugar tolerance curves were higher and more prolonged than normal. They suggested that the infrequent glycosuria is due to a high renal threshold, an inference that might account for the supposed high carbohydrate

28. Lloyd, P. C.: A Case of Hypophyseal Tumor with Associated Tumor-Like Enlargement of the Parathyroids and Islands of Langerhans, Bull. Johns Hopkins Hosp. **45**:1 (July) 1929.

29. Bodansky, A.; Sutherland, S., and Goldberg, S.: A Case of Hyperglycemia in a Thyroidectomized Sheep, Proc. Soc. Exper. Biol. & Med. **20**:195, 1922. Werner, G.: Variations de la glycémie et de la séro-calcémie dans le syndrome athyroïdien expérimental, Compt. rend. Soc. de biol. **100**:926 (April 8) 1929.

30. Sharpey-Schaffer, Sir E.: The Endocrine Organs, ed. 2, London, Longmans, Green & Company, pt. 2, p. 35.

31. Campbell, J. W.: Low Blood Sugar in Hypothyroid Conditions, J. Kansas M. Soc. **30**:365 (Nov.) 1929.

32. Gray, H.: Blood Sugar Standards: II. In Conditions Neither Normal nor Diabetic, Arch. Int. Med. **31**:259 (Feb.) 1923.

33. Gardiner-Hill, H.; Brett, P. C., and Smith, J. F.: Carbohydrate Tolerance in Myxoedema, Quart. J. Med. **18**:327 (April) 1925.

tolerance of myxedematous persons. In their experience thyroid extract did not raise the level for sugar during fasting, but brought the sugar tolerance curves down toward normal. One may assume, then, that certain myxedematous patients may exhibit hypoglycemia, but the degree is not great and is usually not responsible for symptoms.

PLURIGLANDULAR SYNDROMES

(*a*) Under the title, "Suprarenal Insufficiency with Dysinsulinism," Gougerot and Peyre[34] described six persons with pigmentation, hypotension and feebleness before meals associated with mild hypoglycemia (from 67 to 56 mg.) and relieved by sugar. Syphilis was considered to play an important causative rôle. No fatalities occurred. No pathologic data were given.

(*b*) Longcope[22] reported hypoglycemic attacks in a man with scleroderma who had a bronzed skin, hypotension and a low basal metabolic rate. He drew attention to the similarity to Addison's disease. Thyroid extract improved the scleroderma and elevated the metabolism, but had no effect on the blood sugar or the attacks.

(*c*) Stenström[13] described a young woman, amenorrheic, without axillary or pubic hair and with scant eyebrows, who suffered a single attack of hypoglycemic coma. The basal metabolic rate was low. She was brought out of a rigid coma by the injection of epinephrine, and was kept free from attacks, with normal blood sugar, by the administration of suprarenal and thyroid extracts.

(*d*) In a somewhat similar case of Petterson's,[35] a young woman, amenorrheic and with scant hair, lapsed into hypoglycemic coma. She was revived and had no further seizures, but died three months later with a normal blood sugar. Small pituitary and thyroid glands, with an altered suprarenal cortex and sclerosed ovaries, were found at autopsy. Injection of her blood into a rabbit caused no fall in blood sugar.

OTHER TYPES OF HYPOGLYCEMIA

HEPATIC HYPOGLYCEMIA

In addition to the foregoing discussion of the rôle of the liver in maintaining blood sugar, reference may be made to the excellent work of Mann[36] and his colleagues in clarifying this relation. Hence one

34. Gougerot, H., and Peyre, E.: Suprarenal Insufficiency with Dysinsulinism: New Pluriglandular Syndrome, Compt. rend. Soc. de biol. **93**:1202 (Nov. 20) 1925.

35. Petterson, A. S.: Ein Fall von spontanem hypoglykämischen Koma, Acta med. Scandinav. **69**:232, 1928.

36. Mann, F. C.: The Effects of Complete and of Partial Removal of the Liver, Medicine **6**:419 (Dec.) 1927.

might expect hypoglycemia from destructive lesions of this great glycogen depot. This occurred in a case recently reported by Nadler and Wolfer.[37] A patient whose liver was riddled with carcinoma suffered attacks of extreme hypoglycemia during the last three months of life.

Josephs [38] had previously reviewed the literature of recurrent vomiting in children, finding various degrees of associated hypoglycemia. He was inclined to view the fatty degeneration of the liver found in fatal cases as a possible cause of the hypoglycemic seizures. Certain cases of hypoglycemia in children reported by Griffith [39] and that of Snapper and van Creveld [40] may belong in this group.

Wagner and Parnass,[41] in the first report of clinical hypoglycemia that we have found in the literature, described a child whose only symptoms were weakness and a large abdomen due to a tremendous liver. Glycosuria and hyperglycemia after meals alternated with extreme hypoglycemia and ketonuria on fasting. Although the blood sugar was "absent" at times, no symptoms of shock were noted.

Though we shall not review the hypoglycemic effects of hepatotoxic substances, the observations of Le Count and Singer [42] on alcoholic addicts are pertinent. The fatty infiltration uniformly found in the liver and the death in convulsions of one patient with a blood sugar content of 67 mg. suggested that sudden death in alcoholic persons and "whiskey fits" might be due to hypoglycemia. They considered that the glycogen-storing capacity might be reduced by the fatty infiltration caused by alcohol. This hypothesis must await further study.[43]

MUSCULAR DYSTROPHY

In view of Cori and Cori's hypothesis of muscle glycogen as a source of blood sugar, referred to, one might seek for hypoglycemia in destructive muscular lesions. Scheimann [44] investigated the carbo-

37. Nadler, W. H., and Wolfer, J. A.: Hepatogenic Hypoglycemia Associated with Primary Liver Cell Carcinoma, Arch. Int. Med. **44**:700 (Nov.) 1929.

38. Josephs, H.: Spontaneous Hypoglycemia in Childhood, Am. J. Dis. Child. **38**:746 (Oct.) 1929.

39. Griffith, J. P. C.: Hypoglycemia and the Convulsions of Early Life, J. A. M. A. **93**:1526 (Nov. 16) 1929.

40. Snapper, L., and van Creveld, S.: Un cas d'hypoglycémie avec acétonémie chez un enfant, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:1315 (July 26) 1928.

41. Wagner, R., and Parnass, J. K.: Ueber eine eigenartige Störung des Kohlen Draststoffwechsels, Ztschr. f. d. ges. exper. Med. **25**:361, 1921.

42. Le Count, E. R., and Singer, H. A.: Fat Replacement of the Glycogen in Liver as a Cause of Death, Arch. Path. **1**:84 (Jan.) 1926.

43. Cammidge, P. J.: Hypoglycaemia, Lancet **2**:1277 (Dec. 20) 1924.

44. Scheimann, M. S.: Der Kohlenhydratumsatz bei der Dystrophia musculorum progressiva, Arch. f. Psychiat. **87**:655, 1929.

hydrate metabolism in eight persons with progressive muscular atrophy, and found two with hypoglycemic levels. No symptoms of shock appeared.

RENAL DIABETES

Many authors have found a tendency toward low blood sugar in renal diabetes.[45] Usually the degree of depression is slight and no symptoms are associated. The sugar lost in the urine apparently is not responsible, for excretion of large amounts of sugar is not always associated with shock.[46] Mild symptoms from the hypoglycemia occurred in Gibson and Larimer's [47] patient. Certain of the fifty cases of mild hypoglycemia studied by Hoxie and Lisherness [48] probably were due to renal glycosuria.

LACTATION AND PREGNANCY

Hypoglycemic seizures in a nursing mother who also had pulmonary tuberculosis and valvular heart disease were delineated by Stenström.[49] The attacks were lessened by cutting down the high amount of fat in the diet, and eliminated by weaning the child. After weaning, the same diet no longer produced the seizures.

Relative hypoglycemia associated with eclampsia was observed by Titus, Willetts and Lightbody.[21] Sharp drops in the blood sugar preceding convulsions were noted, but the level of hypoglycemia was not low. A rise of blood sugar followed the convulsion. It seems unlikely that the convulsion results from the hypoglycemia.

FATIGUE

Physical exhaustion in marathon runners is attributed to the production of hypoglycemia by Levine, Gordon and Derick.[50] Less conspicuous are the cases of hypoglycemia from chronic fatigue, but many of Hoxie and Lisherness' [48] cases could be explained on no other basis.

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45. Jonas, L.: Renal Glycosuria, M. Clin. North America **6**:1079 (Jan.) 1923. Gibson, R. B., and Larimer, R. N.: Hypoglycemic Symptoms Provoked by Repeated Glucose Ingestion in a Case of Renal Diabetes, J. A. M. A. **82**:468 (Feb. 9) 1924.

46. Jonas (footnote 45, first reference).

47. Gibson and Larimer (footnote 45, second reference).

48. Hoxie, G. H., and Lisherness, G. M.: Hypoglycemia, Am. J. M. Sc. **173**: 220 (Feb.) 1927.

49. Stenström, T.: Spontane hypoglykämische Reaktion bei stillender Frau, Deutsches Arch. f. klin. Med. **153**:181, 1926.

50. Levine, S. A.; Gordon, B., and Derick, C. L.: Some Changes in the Chemical Constituents of the Blood Following a Marathon Race, J. A. M. A. **82**:1778 (May 31) 1924.

INFECTIONS

Certain infections, such as diphtheria, cholera, typhoid, late tuberculosis and experimental trypanosomiasis, are accredited by some writers with producing hypoglycemia. It is not within our scope in this paper to investigate extraneous causes of hypoglycemia.

TERMINAL HYPOGLYCEMIA

Terminal hypoglycemia in diabetes has already been mentioned. Ashe, Mosenthal and Ginsberg [51] discussed a case in which the patient died in uremia with a blood sugar level of 30 mg.

SUMMARY

Hypoglycemia may result from several types of abnormal mechanisms: (1) from disturbance of carbohydrate control (*a*) through overproduction of insulin by hyperfunction, hypertrophy or tumor of the islets or (*b*) through loss of the substances that are antagonistic to insulin as in hypo-adrenalinism, hypothyroidism, pituitary dysfunction or combinations of these; (2) from interference with storage or release of glycogen in the depots of the body—the liver and muscles—or from depletion of glycogen from physical effort; (3) from conditions in which dextrose is lost from the body as such, e. g., in renal diabetes, or as other sugar, e. g., in lactation. The most important cause, by far, is that of overproduction of insulin.

In attempting to distinguish the various types of hypoglycemia, one must look for concomitant evidence of disorders of the endocrine glands or glycogen depots or of the loss of carbohydrate. Hypoglycemia of pancreatic origin presents a typical syndrome recognized without difficulty.

The point of distinction between hypoglycemic seizures and other convulsive states rests on the depressed blood sugar level. A history of relief from the ingestion of food often suggests this investigation.

A review of the clinical manifestations of pancreatic hypoglycemia has been attempted, based on the cases reported in the literature. A typical case of hyperinsulinism has been added to this group. In order to contrast pancreatic with other forms of hypoglycemia, examples of the various types of spontaneously appearing hypoglycemia have been cited. Outlines of the details of the available reports of pancreatic hypoglycemia and of leading cases of the other types are given in the accompanying tables.

51. Ashe, B. I.; Mosenthal, H. O., and Ginsberg, G.: Hypoglycemia: With and Without Insulin; With and Without Symptoms, J. Lab. & Clin. Med. **13**:109 (Nov.) 1927.

THE EFFECT OF HIGH ALTITUDES ON THE CHOLESTEROL, LECITHIN AND FATTY ACIDS IN THE PLASMA OF HEALTHY MEN *

GULLI LINDH MULLER, M.D.
AND
JOHN H. TALBOTT, M.D.
BOSTON

In many clinical conditions involving the hematopoietic organs, cholesterol and lecithin show deviation from the normal, indicating that in some way, directly or indirectly, the metabolism of these substances may be intimately related to the functioning of the blood-forming tissues.[1] A very small amount of data is available, however, which definitely correlate a functional physiologic state of the hematopoietic organs with the lipoids of the blood.

It is well known that exposure to low barometric pressure, that is, to low oxygen tension, will cause a stimulation of the blood-forming organs. This has been repeatedly verified [2] since Viault [3] demonstrated that the peripheral blood of man in passing from a low to a high altitude shows an increase of red blood cells and hemoglobin. Zuntz and his associates [4] and Dallwig, Kolls and Loevenhart [5] also found evidences of stimulation of the bone marrow in animals subjected to low oxygen tension. From their experiments they concluded that "the bone marrow has no power to adapt itself to decreased oxygen supply since the increased rate of erythrocytes and haemoglobin formation continue indefinitely for a given oxygen tension." This has been substantiated from a different angle by the results of Barcroft and the other members of the Cerro de Pasco Expedition [6] who demonstrated that at an alti-

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* From the Thorndike Memorial Laboratory of the Boston City Hospital, and the Leadville Expedition from the Harvard Fatigue Laboratory, D. B. Dill, Director.

* Anna Ryan, A. B., gave us technical assistance.

1. Muller, G. L.: Medicine **9**:119, 1930.
2. Schneider, E. C.: Physiol. Rev. **1**:631, 1921.
3. Viault, F.: Compt. rend. Acad. d. sc. **111**:917, 1890; **114**:1562, 1892.
4. Zuntz, N.; Loewy, A.; Müller, F., and Caspari, W.: Höhenklima und Bergwanderungen, Berlin, Bong & Company, 1906.
5. Dallwig, H. C.; Kolls, A. C., and Loevenhart, A. S.: Am. J. Physiol. **39**: 77, 1915-1916.
6. Barcroft, J.: The Respiratory Function of the Blood: I. Lessons from High Altitudes, London, Cambridge University Press, 1925.

tude of 14,200 feet, concomitant with the increase of red cells and hemoglobin in the blood, there was an increase of reticulocytes to about 4.9 per cent in normal persons. However, an increase of the absolute number of reticulocytes was also found constantly in the permanent residents of the region, and it was concluded that the rate of production of red blood cells from a given quantity of bone marrow was the same, but that in high altitudes the active bone marrow was increased in volume. Barcroft and his associates thought, therefore, that the reticulocytes are probably not extruded in greater numbers than correspond to the increase of the number of erythrocytes in the peripheral blood.

All the evidence thus points to an active stimulation of the blood-forming organs or to an extension of the normally functioning bone marrow when man or animals are subjected to low oxygen tension.

EXPERIMENTAL WORK

This paper deals with the amount of cholesterol, lecithin and fatty acids in the blood of four healthy young men during an expedition to Mount Elbert, Colorado, in the summer of 1929. The ascent to the 10,000 foot level was made by automobile or train, and from the 10,000 foot level to the 14,000 foot level by horse most of the way. The lipoids have been correlated with the oxygen capacities of the blood as a measure of the functioning hemoglobin, and occasionally with the red blood cell count. Material for the determinations was collected by members of the expedition at a 10,000 foot level, and in two of the subjects, for a short time, at a 14,000 foot level. Specimens of the blood were taken twelve hours after arrival on the mountain at the 10,000 foot level but, unfortunately, control determinations at sea level were not obtained before the ascent. Determinations of the lipoids on three of the subjects at sea level were made one year later in the early summer of 1930 so as to exclude any possible seasonal effect.[7] The cholesterol was determined by the method of Bloor, Pelkan and Allen,[8] the lipoid phosphorus by the method of Whitehorn[9] and the oxygen capacity by the method of Van Slyke.[10] The results obtained are set forth in the tables with explanatory data.

The examination of these tables revealed that with the methods used no demonstrable change occurred in the amount of cholesterol during the stay at the 10,000 or the 14,000 foot level. One subject seemed to show a slight fall of the lecithin phosphorus during the first week of

7. Currie, A. N.: Brit. J. Exper. Path. **5**:293, 1924.

8. Bloor, W. R.; Pelkan, K. F., and Allen, D. M.: J. Biol. Chem. **52**:191, 1922.

9. Whitehorn, J. C.: J. Biol. Chem. **62**:133, 1924.

10. Van Slyke, D. D., and Stadie, W. C.: J. Biol. Chem. **49**:1, 1921.

TABLE 1.—*Lipoids and Oxygen Capacity of Blood in A. F.*

Days	Cholesterol, Mg. per 100 Cc. Plasma	Lecithin Phosphorus, Mg. per 100 Cc. Plasma	Fatty Acids, Mg. per 100 Cc. Plasma	Oxygen Capacity, per Cent by Volume	Red Blood Cells, per C.Mm.	Time of Obtaining Blood Sample	Comment
1	170	8.8	377	20.10	5,670,000	9:00 a.m.	10,000 feet above sea level; first blood sample taken 12 hours after arrival
2	170	8.3	357	20.80	4,680,000	9:00 a.m.	
3	152	9.2	480	20.96	5,880,000	9:00 a.m.	
4	163	9.8	374	20.60	4,970,000	9:00 a.m.	
5	159	10.0	441	20.88	5,190,000	9:00 a.m.	
6	166	8.9	416	20.93	5,140,000	9:00 a.m.	
8	182	9.1	445	20.45	5,720,000	9:00 a.m.	
11	169	10.8	415	21.85	.....	9:00 a.m.	
21	167	10.1	389	20.77	.....	10:00 a.m.	
24	178	9.9	422	21.33	.....	2:30 p.m.	
0	170	9.4	442	19.80	.....	3:30 p.m.	14,000 feet above sea level
1	163	8.7	441	19.80	.....	3:00 p.m.	First blood sample taken 1 hour after arrival; subject rode horseback to the top
2	157	9.1	422	19.25	.....	1:00 p.m.	
13	...	...	...	19.65	.....	.....	10,000 feet above sea level

TABLE 2.—*Lipoids and Oxygen Capacity of Blood in A. M. P.*

Days	Cholesterol, Mg. per 100 Cc. Plasma	Lecithin Phosphorus, Mg. per 100 Cc. Plasma	Fatty Acids, Mg. per 100 Cc. Plasma	Oxygen Capacity, per Cent by Volume	Red Blood Cells, per C.Mm.	Time of Obtaining Blood Sample	Comment
1	153	7.5	361	21.67	4,760,000	9:00 a.m.	10,000 feet above sea level; first blood sample taken 12 hours after arrival
2	142	7.5	425	21.72	4,970,000	9:00 a.m.	
4	133	7.4	418	20.49	4,950,000	9:00 a.m.	
5	152	7.1	434	20.54	.....	9:00 a.m.	
6	160	7.3	460	20.78	.....	9:00 a.m.	
7	150	7.9	403	21.83	.....	9:00 a.m.	
8	149	8.8	422	21.97	.....	9:00 a.m.	
13	173	7.8	441	21.25	.....	9:00 a.m.	
16	144	7.8	476	20.98	.....	10:00 a.m.	Arterial blood
19	...	...	...	20.33	.....	.....	
20	156	8.3	508	19.87	.....	2:30 p.m.	
0	152	10.3	483	20.60	.....	3:30 p.m.	14,000 feet above sea level
1	135	9.4	476	20.49	.....	3:00 p.m.	First blood sample taken 1 hour after arrival
2	139	8.3	467	20.25	.....	1:00 p.m.	Subject rode horseback to top
4	153	9.0	469	20.66	.....	7:00 a.m.	
16	...	...	...	22.10	.....	.....	10,000 feet above sea level
1	127	9.3	424	.....	.....	9:00 a.m.	Sea level
3	...	10.8	405	.....	.....	9:00 a.m.	
8	123	9.2	408	.....	.....	9:00 a.m.	
10	126	9.1	457	.....	.....	9:00 a.m.	

his residence at the 10,000 foot level (table 3), while a slightly higher level of lecithin phosphorus was observed at the 14,000 foot level in another (table 2) than at the 10,000 foot level. These variations, however, are slight and not uniform. Neither can any significant change be demonstrated in the oxygen capacity of the blood that can be ascribed to the change of the oxygen tension of the air.

TABLE 3.—*Lipoids and Oxygen Capacity of Blood in J. H. T.*

Days	Cholesterol, Mg. per 100 Cc. Plasma	Lecithin Phosphorus, Mg. per 100 Cc. Plasma	Fatty Acids, Mg. per 100 Cc. Plasma	Oxygen Capacity, per Cent by Volume	Red Blood Cells, per C.Mm.	Time of Obtaining Blood Sample	Comment
1	166	8.6	377	22.45	5,680,000	9:00 a.m.	10,000 feet above sea level; first blood sample taken 12 hours after arrival
2	150	9.1	361	22.55	5,460,000	9:00 a.m.	
3	179	8.2	393	23.23	5,780,000	9:00 a.m.	
4	163	8.4	322	21.55	5,860,000	9:00 a.m.	
5	170	7.9	373	22.88	5,710,000	9:00 a.m.	
6	178	7.7	405	23.76	5,600,000	9:00 a.m.	
8	169	7.0	338	23.27	5,340,000	9:00 a.m.	
9	153	7.5	344	21.85	.....	9:00 a.m.	
11	...	...	...	23.26	.....	9:00 a.m.	
13	150	8.3	358	24.18	.....	9:00 a.m.	
17	142	8.3	357	21.74	.....	9:00 a.m.	
39	...	...	...	22.69	.....	.....	
1	195	8.7	454	.....	.....	9:00 a.m.	Sea level
2	188	8.4	434	.....	.....	9:00 a.m.	
3	184	8.0	405	.....	.....	9:00 a.m.	
4	197	8.7	405	.....	.....	9:00 a.m.	

TABLE 4.—*Lipoids and Oxygen Capacity of Blood in D. B. D.*

Days	Cholesterol, Mg. per 100 Cc. Plasma	Lecithin Phosphorus, Mg. per 100 Cc. Plasma	Fatty Acids, Mg. per 100 Cc. Plasma	Oxygen Capacity, per Cent by Volume	Time of Obtaining Blood Sample	Comments
1	133	7.9	425	19.65	9:00 a.m.	10,000 feet above sea level
2	132	8.1	438	20.00	9:00 a.m.	First blood sample taken 12 hours after arrival
3	135	8.2	426	19.71	9:00 a.m.	
4	134	7.7	416	19.87	9:00 a.m.	
21	...	...	...	20.68	9.00 a.m.	
1	145	7.9	395	.....	9:00 a.m.	Sea level
3	141	8.1	395	.....	9:00 a.m.	
8	143	7.9	408	.....	9:00 a.m.	
11	144	7.7	438	.....	9:00 a.m.	

In the three subjects in whom the lipoids of the blood were determined at the sea level, the average cholesterol values, when compared with those obtained on Mount Elbert, were slightly higher in two and lower in one. These results thus are contradictory, and whether any significance can be attached to them is problematic. It is, however,

noteworthy that the amounts of cholesterol in healthy men vary considerably from each other, but that they are regulated at a particular level during a given period in the same person in a fairly constant manner.

The lecithin phosphorus in two subjects was practically the same at sea level and at the 10,000 foot level. In a third subject (table 3) the average lecithin phosphorus was 7.7 mg. per hundred cubic centimeters of plasma at the 10,000 foot level and 9.2 mg. at the 14,000 foot level, as contrasted with 9.6 mg. per hundred cubic centimeters at sea level. No trend that seemed of any significance could be made out in the level of the fatty acids.

COMMENT

A very small amount of data is available on the lipoids of the blood in high altitudes. Rabbeno,[11] making determinations on himself, came to the conclusion that on Col d'Olen (altitude 10,000 feet) the cholesterol remained unchanged for from three to four days, and then increased. This phenomenon was more marked in November than in the summer months, so that the lower temperature must be considered as well as the rarefaction of the air. Schemensky,[12] studying his own blood at sea level and at Davos (altitude about 5,100 feet), thought that there was a slightly higher cholesterol level at Davos. From the examination of his figures, however, there does not seem to be any clearly established change. His examinations include two other persons with one determination each at Berlin and at Davos which showed respectively 135 and 165 mg. per hundred cubic centimeters of plasma at Berlin and 178 and 246 mg. per hundred cubic centimeters of plasma at Davos. Four residents at Davos gave values between 235 and 481 mg. of cholesterol per hundred cubic centimeters of plasma (one determination each) while two tuberculous patients had 195 and 246 mg. per hundred cubic centimeters of blood. Schemensky concluded that in high altitudes there are greatly increased values of cholesterol, almost equal to those seen in nephritis. Decreased atmospheric pressure alone caused no change in cholesterol in animals, but one dog exposed to sunlight had a marked increase of cholesterol in the blood. Schemensky therefore suggested that light may play some part. Guinea-pigs at sea level had from 30 to 40 mg. of cholesterol per hundred cubic centimeters, while guinea-pigs at Davos showed from 71 to 88 mg. per hundred cubic centimeters of blood. As the altitude of Davos is only about 5,000 feet, distinct physiologic changes due to decreased oxygen tension are not

11. Rabbeno, A.: Arch. di sc. biol. **9**:161, 1926; abstr., Ber. u. d. ges. Physiol. **40**:409, 1927.

12. Schemensky, W.: Ztschr. f. klin. Med. **111**:205, 1929.

to be expected. On the other hand, Sundstroem and Bloor [13] reported a decrease of the lipoid phosphorus of approximately 13.2 per cent in animals subjected to low barometric pressure. They suggested that the first phase of stimulation of the bone marrow resulting from a lowering of the oxygen tension is an enrichment of the erythropoietic organs with lipoid material.

From our data it may be concluded that, with the methods used, no consistent significant change can be demonstrated in the amount of lipoids in the blood of healthy men subjected to low barometric pressure at altitudes of 10,000 and 14,000 feet. This may be due to the fact that an altitude of 10,000 feet is too low to produce any marked physiologic changes, as suggested by Barcroft,[6] and that the residence of our subjects at the 14,000 foot level was of too short duration. As no marked stimulation of the hematopoietic organs was observed, as evidenced by the unchanged level of red blood cells and hemoglobin (reticulocyte counts were not made), the results obtained do not throw any light on the relation between increased blood formation under physiologic conditions and the lipoids of the blood.

CONCLUSIONS

Cholesterol, lecithin phosphorus, fatty acids and the oxygen capacity of the blood were determined in four healthy men at sea level and during several days' residence in Leadville, Colorado, 10,000 feet above sea level, and later in two subjects at Mount Elbert at a 14,000 foot level. No consistent significant changes were observed in these constituents of the blood that could be ascribed to the high altitude.

13. Sundstroem, E. S., and Bloor, W. R.: J. Biol. Chem. **45**:153, 1920.

A BIOMETRICAL ANALYSIS OF TWO THOUSAND, FIVE HUNDRED AND SIXTY-TWO COMPLETE EXAMINATIONS OF THE BLOOD*

EDGAR T. HERRMANN, M.D.
ST. PAUL

Estimations of the hemoglobin and morphologic constituents of the blood have been determined on large groups of normal persons under varying conditions. Further statistical inquiry would be useless, yet there are certain data, acquired in semipathologic investigations, that are still open to fruitful inquiry. It is with events of this sort that the present paper concerns itself.

There is a large group of ambulant persons, neither ill nor well, who every day subject themselves to medical inquiry. Among them major physical damage is the exception, and subjective functional disturbance the rule. They are the people with elusive focal infection, malnutrition, disturbed gastro-enterologic function, neurocirculatory asthenia, etc. Persons of this type as well as others with organic lesions in whom no marked changes in the blood were evident form the basis for the present survey. No frank diseases of the blood or other unusual variants were included in the 2,562 cases here recorded. Marked leukocytosis or leukopenia, over 15,000 or below 4,000, was ruled out. Sharp anemias or polycythemic conditions were likewise not included.

The object in the present study was to measure the frequency distribution in the variation of the separate elements concerned in an examination of the blood by determining the constants which would give a sufficient picture of the central or typical condition with respect to each element. The three constants ascertained for each element were, in turn, the arithmetical mean, the median and the mode. By definition the mean supplies the center of gravity of the frequency distribution, the median is the value above and below which exactly 50 per cent of the variates fall, while the mode establishes a figure exhibiting the maximum frequency of occurrence. The degree of scatter of the observed variates was determined by the computation of the standard deviation as well as the general coefficient of variation in each case. The significance of the established constants was checked by the estimation of the probability of error in the case of both the mean and the median for all observed elements. It was hoped that in this way true values could be

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* From the Miller Hospital Clinic.

established and the comparative accuracy of the arithmetical mean for observations of this type be determined. The first effort, then, was directed toward giving as true an account as possible of the complete blood picture occurring not in the normal subject, but in the average ambulant patient seeking medical advice. Further, it was hoped that it would also appear whether or not there was a seasonal or other rhythmic variation observable in time, affecting any or all of the constituents of the blood examined. Because of the nature of the problem, a time interval of two years was chosen, the dividing unit in each case being the month. In the charts the number of cases will be found on the abscissal line just above the respective month.

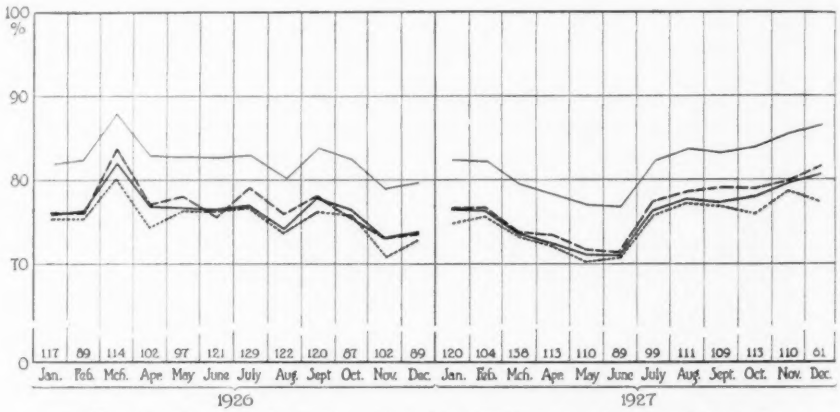

Chart 1.—Mean (solid line), median (dash line) and mode (dotted line) for hemoglobin. The mean range was between 71.0 and 82.1 per cent.

In general, the examinations were made from two to three hours after breakfast, on an empty stomach, between 11 a. m. and 2 p. m. Throughout the series no more than three observers were concerned, all competent and all trained by the same person. A Dare hemoglobinometer was used in estimating hemoglobin values, and the Burker counting chamber with respective pipets was employed for determinations of red blood cells and leukocytes. Differential counts were made in all cases from slides colored with Wright's stain, and 200 cells were counted.

The Dare instrument used reads between 90 and 95 per cent for red blood cell values of 5,000,000 per cubic millimeter. On a scale of 100 per cent this means that the observed readings fall 6 points low. Chart 1 shows the degree of variation obtained. The arithmetical mean is seen here to fall between the median, which usually lies from 0.5 to

3 per cent above it, and the mode, lying somewhat less than that below it. The narrow, unbroken line running parallel to the mean and 6 points above it represents the theoretical hemoglobin value in these cases on the basis of a 100 per cent reading for 5,000,000 red blood cells. The mean range throughout the two years is practically 10 per cent. Two interesting features emerge clearly from the graph. The first is the low average for hemoglobin encountered, actually 76 per cent, and on the corrected scale only 81 per cent. Such figures do not, of course, signify anemia even though they are somewhat low. The next interesting thing is the observed difference in the readings of the mean, median and mode. Estimation of probable errors establishes the recorded differences as

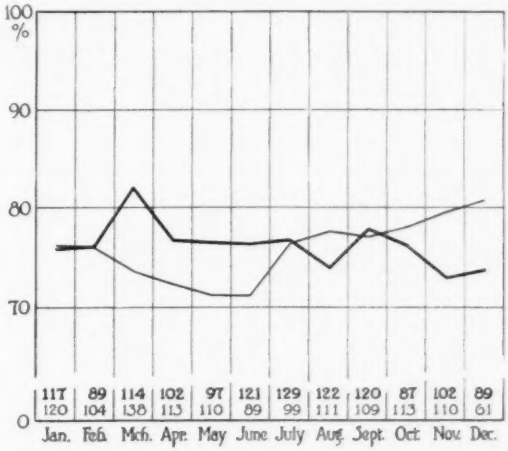

Chart 2.—The 1926 (heavier line) and 1927 (lighter line) means for hemoglobin.

significant. Chart 2 is a visual portrayal of the mean variation curves throughout the two years. It is at once apparent that no similarity of variation obtains in relation to the monthly time interval.

What has been said of the hemoglobin values applies with equal point to the erythrocytes. Chart 3 represents the observed variation of these. All of the readings lie below the accepted normal figure for men, and in every month but one they are under 4,500,000. Here, too, the difference in the three constants is brought out significantly in May, 1926, when an interval of almost 500,000 separates the mode and the median. The subjoined tables of probability of error again establish the differences as real. Chart 4 shows that there is no rhythmic variation present from month to month.

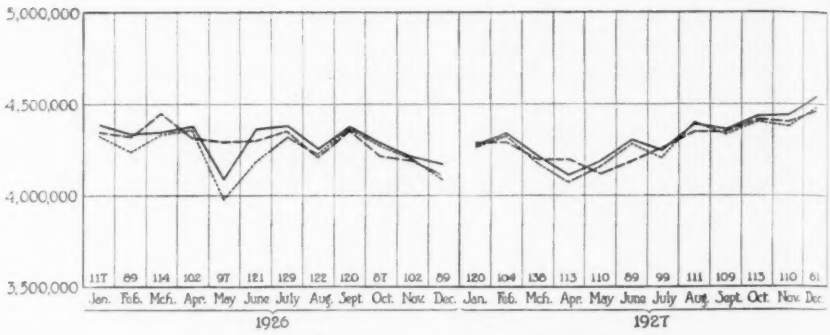

Chart 3.—Mean (solid line), median (dash line) and mode (dotted line) for red blood cells. The mean range was between 4,080,000 and 4,540,000.

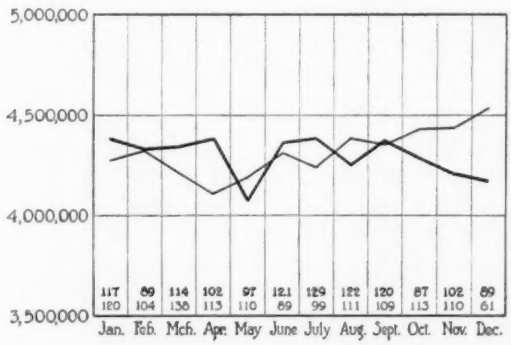

Chart 4.—The 1926 (heavier line) and 1927 (lighter line) means for red blood cells.

The extreme lability of myeloid function makes any total leukocytic variation subject to much conditional interpretation. Thus the daily leukocyte count has been shown to change with the hours. Ellermann and Erlandsen demonstrated a variation of from 7,400 to 10,000 white cells from 6 a. m. to 7 p. m., while Shaw held that there are two leukocytic tides during the twenty-four hours, both reaching their flood soon after noon and midnight. He doubted the existence of digestive leukocytosis, since his curves were independent of food, exercise and sleep. In chart 5, the mean range is from 7,280 to 9,060 for the two years. Here also the arithmetical mean presents a high figure and the median a low one, while the mode falls between the two. The average of the

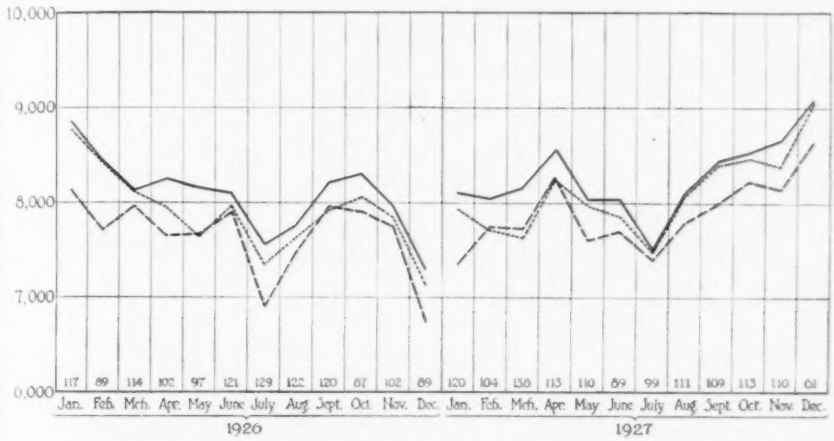

Chart 5.—Mean (solid line), median (dash line) and mode (dotted line) for leukocytes. The mean range was between 7,280 and 9,060.

arithmetical mean over two years is established at 8,160 cells, or somewhat higher than the usual normal value. This tendency to lie above rather than below the normal value may bear some relation to mild, chronic infection, a question more thoroughly considered later. Chart 6 shows that there is, in fact, a partial symmetry of variation in the two years. From March to October the curves follow one another rather closely, an interesting circumstance. On the other hand, the months of November and December show a wide difference, the meaning of which at present remains unclear.

The differential leukocyte values are here recorded only as two large groups: the polymorphonuclear elements and a second group termed lymphoid cells. Under the latter heading are included small and large

lymphocytes as well as the cells at present classified as monocytes. This was done for two reasons: 1. Wright's stain was used, and with this stain the differentiation between the large lymphocyte and monocyte is at best not always easy. The stain of choice would have been a modified Giemsa, which was not used in the laboratory throughout the period of observation. 2. The derivation and classification of the monocyte is at this time the subject of much discussion among hematologists, and for statistical purposes errors of morphologic classification were sedulously avoided. Briefly, the derivation of the monocyte has champions for three different points of origin. Naegeli [1] held to their myeloid origin, Bergel [2] to their lymphoid origin and Schilling [3] to their origin from the

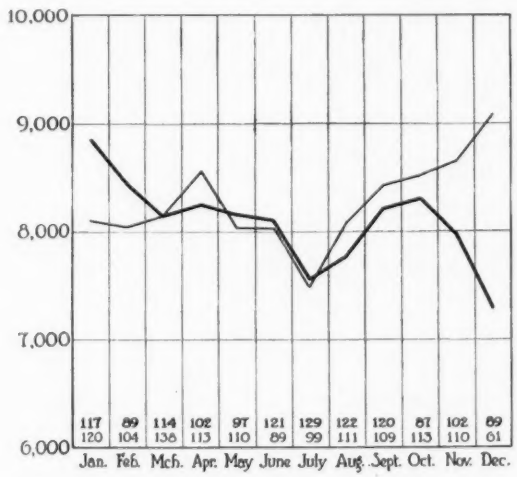

Chart 6.—The 1926 (heavier line) and 1927 (lighter line) means for leukocytes.

reticulo-endothelial cells. Finally, Kiyono [4] and Mosczytz [5] felt that they may be derived from all three. These considerations led to the adoption of the term lymphoid as covering, in the main, the large mononuclear cell, the transitional cell and the very large lymphocyte. It will be found that the recorded percentage of these, taken together with

1. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Berlin, Julius Springer, 1923.

2. Bergel, S.: Die Lymphozytose, Berlin, Julius Springer, 1921.

3. Schilling, V.: Das Blutbild und seine klinische Verwertung, Jena, Gustav Fischer, 1926.

4. Kiyono, K.: Die vitale Karminspeicherung, Jena, Gustav Fischer, 1924.

5. Mosczytz, N.: Ztschr. f. klin. Med. **106**:582, 1927.

that of the polymorphonuclear cells, roughly averages 97. The remaining percentage represents eosinophils, which have not been graphically shown. Naegeli put the normal percentage of lymphocytes at from 20 to 25, of polymorphonuclears at from 65 to 70, and of monocytes at from 6 to 8. Schilling raised the normal lymphocytic variation to 35 per cent, while Egorov [6] found the normal value in Moscow to be 37.6 per cent. The present series shows an arithmetical mean average for lymphoid cells of 37.9 per cent, as recorded in chart 7. The present average for polymorphonuclears is 59.8 per cent, which varies sharply from Egorov's value of 49.7 per cent or Schilling's of 67 per cent. The

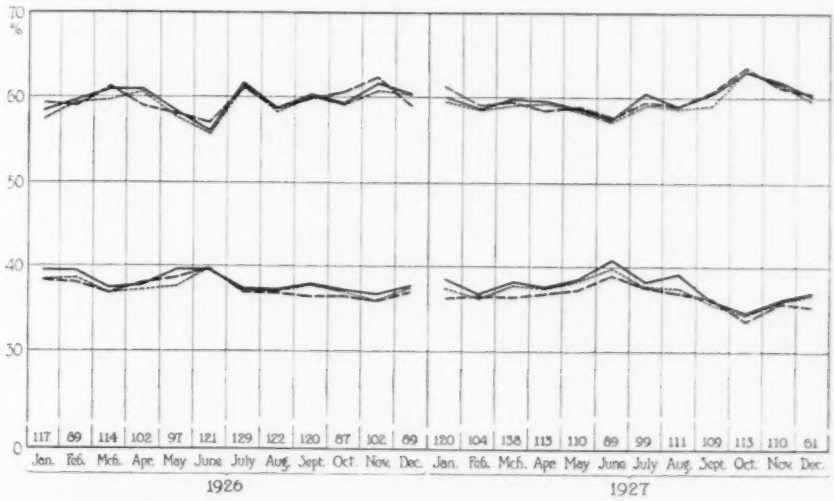

Chart 7.—Mean (solid line), median (dash line) and mode (dotted line) for polymorphonuclears (upper group) and lymphoid cells (lower group). The mean range for polymorphonuclears was between 56.0 and 63.2 per cent; for lymphoid cells, between 34.6 and 40.8 per cent.

difference may be accounted for by geographic variation and different classification. Egorov's lymphocyte percentage, established in 1924, agrees with the present lymphoid average, the difference in the polymorphonuclear percentage indicating principally a variation in monocytes. Taken in conjunction with the polymorphonuclear value, one inclines to the belief that the lymphoid percentage here shown is high. The mean range is between 34.6 and 40.8 per cent. Both Arneth [7] and

6. Egorov: Ztschr. f. klin. Med. **100**:485, 1924; Therap. Arch., 1924, vol. 2.
7. Arneth, J.: Die qualitative Blutlehre, Leipzig, W. Klinkhardt, 1920.

Schilling showed that a moderate lymphocytosis occurs in chronic infections, in the postinfective stages of many maladies and in various types of intoxication. This response is interpreted as a successful reticuloendothelial defense against infection, the holding in check, as it were, of the progress of infection. This point of view seems to be borne out in the present analysis. As stated, many of these patients presented chronic focal infection of one sort or another; many also presented intoxications of postfebrile or other origin. The behavior of the polymorphonuclears is, of course, complementary to that of the lymphoid

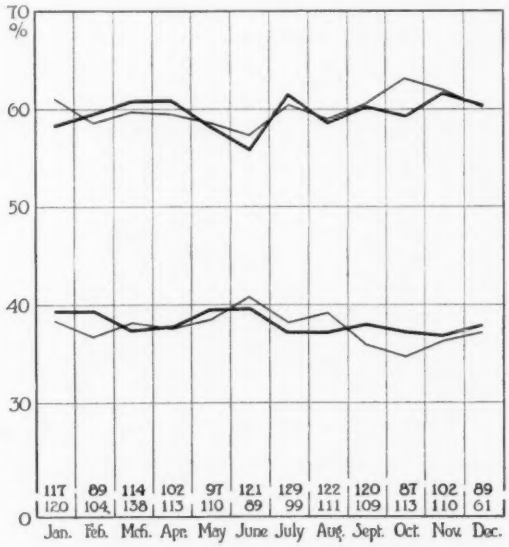

Chart 8.—The upper curves show the 1926 mean (heavier line) and 1927 mean (lighter line) for polymorphonuclears; the lower curves the 1926 and 1927 means for lymphoid cells. Two hundred cells were counted.

cells. In chart 8 a remarkable similar variation is observed over the two-year period with reference to these cells. Thus, May and June of both years show a high peak of lymphoid response, with a gradual declination throughout the rest of the year, while the reverse picture is true of the polymorphonuclear cells. The number of patients examined and the range of variation observed (6 per cent) make one feel that perhaps the obtained evidence of similar variation has some significance. A further study of the coefficients of variation may strengthen this view.

Chart 9 portrays the arithmetical mean averages, together with the probable errors of these averages, for the five elements investigated. For 2,562 cases they show a hemoglobin value of 76.1 per cent (81 per cent on a 100 per cent basis), a red blood cell count of 4,140,000 and a leukocyte count of 8,160.

The differential blood picture shows an average of 59.8 per cent polymorphonuclear cells, 37.9 per cent lymphoid cells and 2.3 per cent eosinophils and basophils.

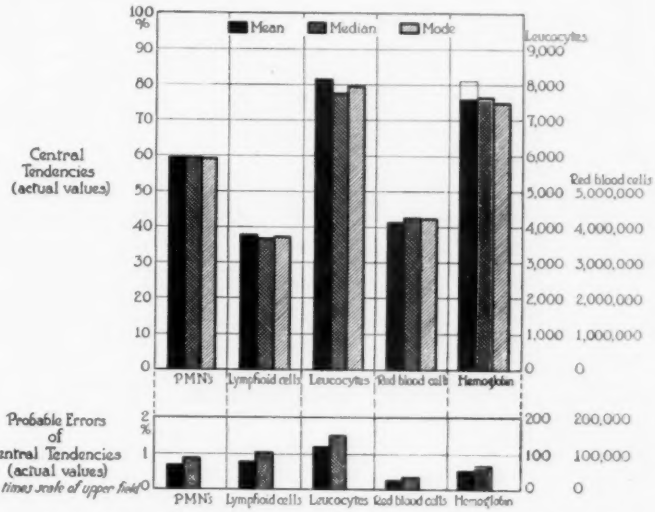

Chart 9.—Arithmetical mean averages, with probable error, for polymorphonuclears (*PMN's*), lymphoid cells, leukocytes, red blood cells and hemoglobin.

CONCLUSIONS

1. The three accepted constants of variation differ significantly when applied to complete examinations of the blood.

2. For data of this kind, the arithmetical mean is a reliable constant.

3. The hemoglobin and erythrocyte values in this group are definitely below normal.

4. The total leukocyte count is perhaps slightly above normal.

5. The percentage of lymphoid cells is above normal, probably because of chronic mild infections and intoxications.

6. There is presumably a significant similar variation, month by month, among polymorphonuclear and lymphoid cells throughout a period of two years.

TABLE 1.—*Constants Determined for Hemoglobin*

Month, 1926	Mean	Median	Mode	Standard Deviation	Coefficient of Variation, per Cent
January	75.8	76.0	75.26	7.57	9.98
February	76.2	76.0	75.46	8.04	10.5
March	82.1	83.6	80.04	10.20	12.5
April	76.7	76.9	74.16	9.17	12.0
May	76.5	77.8	76.43	9.9	12.9
June	76.4	75.6	76.21	8.06	10.5
July	76.9	79.0	76.77	8.82	11.5
August	74.0	75.9	73.58	9.184	12.4
September	77.8	78.0	76.28	9.37	12.0
October	76.5	75.5	75.64	7.50	9.92
November	73.0	73.0	70.72	10.26	13.9
December	73.7	73.5	72.92	8.52	11.8
1927					
January	76.3	76.4	74.87	9.40	12.3
February	76.2	76.5	75.75	8.04	10.5
March	73.5	73.7	73.34	8.90	12.1
April	72.4	73.4	72.08	5.68	9.88
May	71.0	71.5	70.18	8.6	12.1
June	71.0	71.3	70.62	7.35	10.3
July	76.2	77.4	75.84	7.15	9.39
August	77.6	78.7	77.35	5.96	7.68
September	77.2	79.2	77.1	8.21	10.7
October	78.0	79.0	75.94	7.72	9.9
November	79.7	79.9	78.59	6.42	8.06
December	80.7	81.6	77.36	7.21	8.93

TABLE 2.—*Constants Determined for Erythrocytes*

Month, 1926	Mean	Median	Mode	Standard Deviation	Coefficient of Variation, per Cent
January	4,390,000	4,350,000	4,341,000	415,200	9.4
February	4,340,000	4,330,000	4,238,000	352,200	8.11
March	4,350,000	4,450,000	4,342,920	416,000	9.562
April	4,380,800	4,320,000	4,361,820	408,000	9.312
May	4,080,000	4,290,000	3,978,000	457,900	11.2
June	4,360,000	4,300,000	4,194,000	346,000	7.93
July	4,390,000	4,360,000	4,322,000	461,000	10.5
August	4,250,000	4,210,000	4,211,000	411,000	9.68
September	4,380,000	4,350,000	4,377,000	385,000	8.79
October	4,290,000	4,210,000	4,286,000	347,000	8.1
November	4,210,000	4,190,000	4,205,000	340,000	8.09
December	4,170,000	4,110,000	4,094,000	447,000	10.7
1927					
January	4,270,000	4,280,000	4,269,000	393,000	9.21
February	4,330,000	4,280,000	4,325,000	423,000	9.77
March	4,220,000	4,200,000	4,175,720	490,000	11.61
April	4,120,000	4,200,000	4,071,780	480,000	11.65
May	4,180,000	4,120,000	4,156,000	385,000	9.22
June	4,310,000	4,180,000	4,292,000	386,000	8.95
July	4,240,000	4,260,000	4,205,000	452,000	10.7
August	4,390,000	4,350,000	4,391,000	243,200	5.54
September	4,370,000	4,360,000	4,343,000	389,000	8.91
October	4,430,000	4,420,000	4,415,000	424,000	9.79
November	4,440,000	4,410,000	4,388,000	343,000	7.75
December	4,540,000	4,460,000	4,480,000	346,000	7.63

TABLE 3.—*Constants Determined for Leukocytes*

Month, 1926	Mean	Median	Mode	Standard Deviation	Coefficient of Variation, per Cent
January	8,860	8,140	8,773	2,250	25.4
February	8,440	7,740	8,432	1,980	23.5
March	8,120	7,970	8,104	2,440	30.1
April	8,270	7,640	7,948	2,110	25.5
May	8,150	7,660	7,634	2,100	25.8
June	8,110	7,900	7,962	1,840	22.7
July	7,560	6,900	7,346	2,170	28.7
August	7,750	7,480	7,618	2,000	25.9
September	8,200	7,960	7,911	1,760	21.5
October	8,300	7,900	8,049	1,890	22.8
November	7,970	7,760	7,821	1,870	23.4
December	7,280	6,720	7,160	1,520	20.9
1927					
January	8,110	7,350	7,927	2,210	26.0
February	8,040	7,750	7,704	1,960	24.1
March	8,150	7,720	7,622	2,070	25.3
April	8,560	8,260	8,250	2,140	25.0
May	8,030	7,600	7,981	1,900	23.7
June	8,030	7,700	7,843	1,830	22.8
July	7,500	7,380	7,480	1,360	18.2
August	8,110	7,780	8,074	1,744	21.5
September	8,430	7,980	8,396	1,344	16.0
October	8,510	8,209	8,450	1,328	15.6
November	8,650	8,130	8,383	1,784	20.6
December	9,060	8,620	9,050	1,692	18.7

TABLE 4.—*Constants Determined for Polymorphonuclears*

Month, 1926	Mean	Median	Mode	Standard Deviation	Coefficient of Variation, per Cent
January	58.4	59.4	57.44	12.40	21.0
February	59.7	59.0	59.49	10.09	16.9
March	60.9	61.1	59.73	11.54	18.9
April	60.9	58.9	60.53	9.13	15.0
May	58.3	58.1	57.58	12.80	21.9
June	56.0	57.0	55.53	9.32	16.6
July	61.6	61.1	61.34	10.51	17.1
August	48.7	58.7	58.24	10.48	17.9
September	60.2	59.8	59.89	10.15	16.9
October	59.4	60.7	59.34	12.20	20.5
November	61.5	62.3	60.94	10.36	16.9
December	60.3	59.0	60.27	9.25	15.3
1927					
January	60.0	61.3	59.67	8.69	19.6
February	58.6	59.0	58.52	10.20	17.6
March	59.9	59.7	59.01	11.12	18.6
April	59.5	58.5	59.36	11.19	18.8
May	58.6	58.7	58.49	10.69	18.3
June	57.5	57.6	57.30	13.04	22.5
July	60.0	59.5	59.01	9.22	15.4
August	59.0	59.0	58.90	9.58	16.3
September	60.5	60.7	59.20	9.65	16.0
October	63.2	62.8	62.82	9.64	15.2
November	61.9	61.2	61.66	6.68	10.7
December	60.1	60.3	59.62	9.17	15.2

TABLE 5.—*Constants Determined for Lymphoid Cells*

Month, 1926	Mean	Median	Mode	Standard Deviation	Coefficient of Variation, per Cent
January	39.6	38.3	38.3	12.7	32.0
February	39.6	38.0	38.5	12.54	31.7
March	37.4	36.9	36.9	8.4	28.3
April	37.8	38.0	37.1	10.68	28.3
May	39.7	38.7	37.57	12.20	30.5
June	39.7	39.8	39.7	10.21	25.7
July	37.3	37.0	37.2	9.74	26.1
August	37.1	36.9	37.0	10.80	29.1
September	37.8	36.4	37.7	11.58	30.6
October	37.2	36.4	37.0	5.17	25.6
November	36.7	36.0	36.0	9.20	25.1
December	37.8	37.0	37.6	9.80	25.9
1927					
January	38.5	36.2	37.3	12.76	33.0
February	36.8	36.6	36.3	8.29	22.5
March	38.3	36.4	37.8	9.56	24.9
April	37.6	36.9	37.4	11.16	29.7
May	38.7	37.4	38.4	10.60	27.4
June	40.8	39.0	39.9	13.66	33.5
July	38.3	37.7	37.7	8.05	21.0
August	39.2	37.0	37.3	10.49	26.8
September	36.1	36.2	35.6	8.56	23.7
October	34.6	33.6	34.4	7.77	22.7
November	36.2	35.9	36.1	6.72	18.5
December	37.1	35.3	36.9	8.92	24.1

TABLE 6.—*Probable Error of Mean and Median Determined for Hemoglobin*

Month, 1926	Mean	Probable Error, per Cent	Median	Probable Error, per Cent
January	75.8	0.4719	76.0	0.5914
February	76.2	0.5716	76.0	0.7165
March	82.1	0.6443	83.6	0.8080
April	76.7	0.6155	76.9	0.7717
May	76.5	0.6708	77.8	0.8408
June	76.4	0.4968	75.6	0.7840
July	76.9	0.5260	79.0	0.6593
August	74.0	0.5585	75.9	0.7000
September	77.8	0.5723	78.0	0.7170
October	76.5	0.5723	75.5	0.7170
November	73.0	0.7507	73.0	0.9410
December	73.7	0.6193	73.5	0.9120
1927				
January	76.3	0.5810	76.4	0.7280
February	76.2	0.5317	76.5	0.6660
March	73.5	0.5110	73.7	0.6400
April	72.4	0.3654	73.4	0.4580
May	71.0	0.5553	71.5	0.6960
June	71.0	0.5227	71.3	0.6550
July	76.2	0.4850	77.4	0.6070
August	77.6	0.3213	78.7	0.4030
September	77.2	0.5284	79.2	0.6620
October	78.0	0.5060	79.0	0.6220
November	79.7	0.4112	79.9	0.5150
December	80.7	0.6223	81.6	0.7800

TABLE 7.—*Probable Error of Mean and Median Determined for Erythrocytes*

Month, 1926	Mean	Probable Error, per Cent	Median	Probable Error, per Cent
January	4,390,000	0.2600	4,350,000	0.3250
February	4,340,000	0.2532	4,330,000	0.3170
March	4,350,000	0.3060	4,450,000	0.3830
April	4,380,000	0.2720	4,320,000	0.3410
May	4,080,000	0.3120	4,290,000	0.3910
June	4,360,000	0.2130	4,300,000	0.2670
July	4,390,000	0.2762	4,360,000	0.3460
August	4,250,000	0.2435	4,210,000	0.3120
September	4,380,000	0.2372	4,350,000	0.2970
October	4,290,000	0.2603	4,210,000	0.3260
November	4,210,000	0.2270	4,190,000	0.2850
December	4,170,000	0.3193	4,110,000	0.4000
1927				
January	4,270,000	0.2422	4,280,000	0.3040
February	4,330,000	0.2770	4,280,000	0.3470
March	4,220,000	0.2750	4,200,000	0.3450
April	4,120,000	0.3200	4,200,000	0.4010
May	4,180,000	0.2477	4,120,000	0.3170
June	4,310,000	0.2761	4,180,000	0.3460
July	4,240,000	0.3061	4,260,000	0.3837
August	4,390,000	0.1523	4,350,000	0.1906
September	4,370,000	0.2514	4,360,000	0.3150
October	4,430,000	0.2777	4,420,000	0.3480
November	4,440,000	0.2199	4,388,000	0.2760
December	4,540,000	0.2999	4,460,000	0.3750

TABLE 8.—*Probable Error of Mean and Median Determined for Leukocytes*

Month, 1926	Mean	Probable Error, per Cent	Median	Probable Error, per Cent
January	8,860	1.418	8,140	1.780
February	8,440	1.402	7,740	1.760
March	8,120	1.536	7,970	1.930
April	8,270	1.425	7,640	1.790
May	8,150	1.441	7,660	1.810
June	8,110	1.133	7,900	1.420
July	7,560	1.309	6,900	1.640
August	7,750	1.224	7,480	1.530
September	8,200	1.084	7,960	1.360
October	8,300	1.419	7,900	1.410
November	7,970	1.253	7,760	1.570
December	7,280	1.096	6,720	1.370
1927				
January	8,110	1.500	7,350	1.630
February	8,040	1.280	7,750	1.610
March	8,150	1.186	7,720	1.490
April	8,560	1.357	8,260	1.700
May	8,030	1.210	7,600	1.520
June	8,030	1.308	7,700	1.640
July	7,500	0.9238	7,380	1.160
August	8,110	1.117	7,780	1.400
September	8,430	0.8018	7,980	1.000
October	8,510	0.840	8,200	1.983
November	8,650	1.147	8,130	1.440
December	9,060	1.461	8,620	1.830

TABLE 9.—*Probable Error of Mean and Median Determined for Polymorphonuclears*

Month, 1926	Mean	Probable Error, per Cent	Median	Probable Error, per Cent
January	58.4	0.7735	59.4	0.9700
February	59.7	0.7215	59.0	0.9040
March	60.9	0.7290	61.1	0.8333
April	60.9	0.6088	58.9	0.7630
May	58.3	0.6250	58.1	0.7836
June	56.0	0.6088	57.0	0.7530
July	61.6	0.6383	61.1	0.8010
August	58.7	0.6401	58.7	0.8020
September	60.2	0.6252	59.8	0.7840
October	59.4	0.7008	60.7	0.8780
November	61.5	0.6920	62.3	0.8670
December	60.3	0.6583	59.0	0.8350
1927				
January	60.0	0.7280	61.3	0.9120
February	58.6	0.6830	59.0	0.8560
March	59.9	0.6362	59.7	0.7970
April	59.5	0.7128	58.5	0.8940
May	58.6	0.6878	58.7	0.8620
June	57.5	0.9430	57.6	1.180
July	60.0	0.6285	59.5	0.7880
August	59.0	0.6083	59.0	0.7620
September	60.5	0.6177	60.7	0.7740
October	63.2	0.5436	62.8	0.6810
November	61.9	0.3995	61.2	0.5010
December	60.1	0.7922	60.3	0.9930

TABLE 10.—*Probable Error of Mean and Median Determined for Lymphoid Cells*

Month, 1926	Mean	Probable Error, per Cent	Median	Probable Error, per Cent
January	39.6	0.8708	38.3	1.090
February	39.6	0.8870	38.0	1.110
March	37.4	0.5285	36.9	0.6620
April	37.8	0.7088	38.0	0.8880
May	39.7	0.8305	38.7	1.040
June	39.7	0.6388	39.8	0.7950
July	37.3	0.5810	37.0	0.7280
August	37.1	0.6610	36.9	0.8290
September	37.8	0.7190	36.4	0.9022
October	37.2	0.7187	36.4	0.7100
November	36.7	0.6134	36.0	0.7690
December	37.8	0.7100	37.0	0.8900
1927				
January	38.5	0.8353	36.2	1.050
February	36.8	0.5505	36.6	0.7400
March	38.3	0.5490	36.4	0.6680
April	37.6	0.7108	36.9	0.8910
May	38.7	0.6845	37.4	0.8580
June	40.8	0.9766	39.0	1.220
July	38.3	0.3307	37.7	0.4150
August	39.2	0.5309	37.0	0.6660
September	36.1	0.5530	36.2	0.6930
October	34.6	0.4993	33.6	0.6260
November	36.2	0.4120	35.9	0.5200
December	37.1	0.7707	35.3	0.9660

TABLE 11.—*Determination of Constants*

	Z	X	ZX	ZX(2)	ZX(3)	ZX(4)
20	2	1	2	2	2	2
24	8	2	16	32	64	128
28	12	3	36	108	324	972
32	13	4	52	208	832	3,328
36	22	5	110	550	2,750	13,750
40	11	6	66	396	2,376	14,256
44	12	7	84	588	4,116	28,812
48	11	8	88	704	5,632	45,056
52	11	9	99	891	8,019	72,171
56	1	10	10	100	1,000	10,000
60	4	11	44	484	5,324	58,564
64	5	12	60	720	8,640	103,680
68	3	13	39	507	6,591	85,683
76	1	15	15	225	3,375	50,625
84	1	17	17	289	4,913	83,521
	S(Z) 119		S(ZX) 738	S(ZX)² 5,801	S(ZX)³ 53,958	S(ZX)⁴ 560,548

$$V_1 = \frac{S(ZX)}{S(Z)} = 6.20 \qquad V_3 = \frac{S(ZX)^3}{S(Z)} = 453.4$$

$$V_2 = \frac{S(ZX)^2}{S(Z)} = 48.7 \qquad V_4 = \frac{S(ZX)^4}{S(Z)} = 4710.4$$

$\pi_2 = V_2 - V_1^2 = 10.26$

$Mu_2 = \pi_2 - 1/12 \ (= 0.08333) = 10.18$

$a = \sqrt{mu_2} = 3.19$

Standard deviation $= 4 \times 3.19 = 12.76$

Probable error of mean $= X_1$ (where $X = 0.6744898/X$) $\times$ S.D. $= 0.8353$

$\pi_3 = V_3 - 3V_1V_2 + 2\,V_1^3 = 13.062$

$\pi_4 = V_4 - 4V_1V_3 + 6\,V_1^2V_2 - 3V_1^4 = 326.2477$

$Mu_3 = \pi_3 = 13.062$

$Mu_4 = \pi_4 - 1/2\ \pi_2 + \frac{7}{240} \ (= 0.029167) = 320.573367$

$B_1 = \frac{Mu_3^2}{Mu_2^3} = 0.11487$

$B_2 = \frac{Mu_4}{Mu_2^2} = 2.4635$

$X = \frac{\sqrt{B_1}\,(B_2 + 3)}{2\,(5B_2 - 6B_1 - 9)} =$

$d = X \times a = 1.19$

Mode = mean — d = 37.3

Coefficient of variation $= \frac{\text{S.D.}}{\text{mean}} \times 100 = 33$ per cent

Lymphocytes, January, 1927

Estimation of mode, probable error of mean, standard deviation, and coefficient of variation of the mean in per cent

Estimation of median $\frac{0.5}{11} \times 4$ (the class interval) $+ 36 = 36.2$, median

EFFECT OF INTRATHORACIC PRESSURE ON ARTERIAL TENSION *

ELI GRIMES, M.D.
DES MOINES, IOWA

When the intrathoracic pressure is raised above that of the great extrathoracic veins which pass the blood back to the chest, definite changes based on elementary physical principles follow.

If a person shuts off the outlet of air by closing the larynx or nose and lips and makes a forced expiratory effort (blowing), the intrathoracic pressure rises, and the blood cannot flow into the chest; hence, the right side of the heart does not fill, the blood is soon pumped out of the lungs, and the left ventricle likewise becomes empty, arterial circulation is momentarily suspended, and the systolic blood pressure falls to zero.

EXPERIMENTAL PROCEDURE

Experiment 1.—Place within the lips a tube connected with a manometer and make a blowing effort till the manometer registers from 40 to 60. If this can be held for a sufficient length of time there follows a general venous engorgement, the subject becomes cyanotic, the veins stand out, there is a sense of giddiness, and the normal respirations must be begun. At this point the systolic pressure is zero, but after three or four respirations it rises from 50 to 150 above the patient's normal pressure. The explanation of this is evident. The increased intrathoracic pressure shuts the blood out of the heart—the zero phase of pressure—and then, when the intrathoracic pressure is released, the greatly distended veins suddenly empty into the right auricle, the heart is overloaded, the increased volume of blood overdistends the arterial system, and the pressure rises. The rise of pressure depends on the amount of blood, the elasticity of the arteries and the contractile force of the heart. Herein lies the clinical value of this test, namely, the elasticity of the arteries.

It is a principle in physiology that the size of the heart is that of the heart tissues plus the contained blood; therefore, it is possible

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* When these original observations were begun in 1910, there was no literature on the subject. The line of investigation was explained to the medical directors of various life insurance companies. Soon there was published an account of the technic, but the interpretation was not in accord with the facts. No account has been taken of the literature which has since been published.

to measure the relative amount of blood in the heart by determining the change in size. If a silhouette of the heart is taken when the systolic pressure is zero, it is found to be from 25 to 35 per cent smaller than when the respirations are regular, and if another silhouette is taken when the pressure is elevated at the time respirations are resumed, it will be found to be from 35 to 50 per cent larger than under usual conditions.

In the accompanying table, the measurements of the silhouettes of the heart cover a complete cycle of respiration. The size of the heart with the patient at rest is designated as 10.

Blood Pressure and Size of the Heart in Ten Subjects at Rest, on Producing and on Releasing Intrathoracic Pressure

Intrathoracic Pressure Normal: Blood Pressure	Intrathoracic Pressure 50		On Releasing Intrathoracic Pressure	
	Blood Pressure	Heart Measurements	Blood Pressure	Heart Measurements
140 80	0 0	7	170 90	17
130 70	0 0	8	180 90	17
125 80	0 0	6	200 100	18
135 75	0 0	6	240 120	18
145 85	0 0	8	175 90	14
145 75	0 0	7	160 80	15
135 80	0 0	7	150 80	16
140 80	0 0	6	160 90	15
145 85	0 0	8	155 90	14
130 80	0 0	7	140 80	15

The observation that the heart undergoes the same changes in size with a low rebound as it does with a high rebound led to the conclusion that the change in pressure is not due to the condition of the heart or to the volume of blood; therefore, it is due to arterial differences, and the only arterial condition which can cause a variation of pressure is that of elasticity. Other conditions being constant, the elevation in pressure is in inverse ratio to the elasticity of the arteries. Therefore, the respiratory rebound is a measure of the elasticity of the arteries.

PHYSIOLOGIC CONSIDERATIONS

The intrathoracic pressure is a natural accompaniment of hard muscular effort. When a heavy weight is lifted, a heavy blow is struck or a maximum muscular effort of any kind is made, the breath is forcibly held to a point of "getting black in the face." This getting

black in the face is due to the fact that the increased intrathoracic pressure prevents the return of the blood to the chest. The amount of blood in the chest is less than that required for hard muscular work if the breath is held reflexly. Observe a man carrying a heavy weight up a flight of steps; note the infrequency of respirations, his cyanosis and his distended veins; it is evident that he is using more blood than is contained in his chest, or that it returns against the greatly increased intrathoracic pressure. This being the case, there must be an extrathoracic supply of blood, and it can come only from the great vessels of the abdomen. Hence, the intra-abdominal pressure must be at all times as great as the intrathoracic pressure. Otherwise, there would be sudden shutting off of the blood reaching the heart, and prolonged maximum muscular effort would be impossible.

This physiologic deduction led to an investigation of the relation between the intra-abdominal and the intrathoracic pressure, and it was found that the intrathoracic pressure cannot be raised above the intra-abdominal. It is a physiologic necessity that the supply of blood cannot be abruptly shut off from the heart as would be the case if there was no supply outside the chest.

Experiment 2.—A Barnes bag fitted to the end of a small rectal tube is inserted high in the colon; 500 cc. of air is injected into the bag, and the free end of the tube is attached to a manometer. If the subject has been properly prepared by colonic flushing, and if morphine has been administered to prevent peristalsis, the following results are obtained.

When the subject is at rest the intra-abdominal pressure remains near zero, with slight fluctuations, owing to movements of the viscera. When the intrathoracic pressure is raised by the expiratory test, the intra-abdominal pressure rises to the same level. With a manometer tube in the subject's mouth on expiratory effort, the same elevation is recorded by the manometer indicating intrathoracic pressure and the one indicating the intra-abdominal pressure. A laboring man fitted with a colon manometer, as described, recorded an intra-abdominal pressure of 60 when he lifted a 250 pound (114.3 Kg.) weight. When he swung a 50 pound (22.7 Kg.) sledge delivering driving blows on the ground, there was a sudden short rise each time he struck with his breath reflexly held. The intra-abdominal pressure reached as high as 110, demonstrating a terrific stress on the heart.

It was found that while breathing is carried on, the abdominal muscles by their contraction can bring the intra-abdominal pressure much above the intrathoracic, but by no means can the intrathoracic pressure be brought above the intra-abdominal. The important conclu-

sion was reached that the intrathoracic pressure never exceeds the intra-abdominal. This is an important point in the physiology of the distribution of the blood.

When the great volume of venous blood contained in the abdomen, with its liver and spleen and great veins, is considered in connection with the fact that raising the intra-abdominal pressure simultaneously with that of the chest causes marked changes, the inference was made that increasing the intra-abdominal pressure alone would likewise cause changes in the blood pressure. But since abdominal pressure alone would not diminish the supply of blood to the heart, there would be no fall in arterial tension; on the contrary, the supply of blood to the heart would be increased, and therefore, the arterial pressure would be increased. This was found to be the case.

Experiment 3.—If during regular and normal breathing a person voluntarily contracts the abdominal muscles with all the effort possible there follows at once a marked rise in arterial tension. This rise in pressure is conditioned on the degree of effort, the physical type of the subject and the condition of the arteries.

There is a great difference in the degree of effort that different persons can make, as there is a strong tendency for the glottis to close reflexly during "straining," thus increasing the intrathoracic pressure.

Persons who showed a rebound of systolic pressure to 200 on performing the blowing test could raise the blood pressure 20 above the normal pressure when at rest by contracting the abdominal muscles alone. Those showing no abnormal respiratory rebound could not raise their arterial tension by abdominal effort, as a rule, but some whose rebound was normal, that is, not more than 50 above their normal pressure at rest, could raise their systolic pressure 10 points above the normal point at rest. It is therefore evident that the increase of systolic pressure due to abdominal straining is the result of the increased volume of blood that reaches the heart.

It was determined that the ability to increase the systolic pressure by abdominal effort depended on the condition of the arteries, but mainly on the musculature of the individual.

In studying the changes in arterial pressure due to the changing blood volume, an important observation was made on the effect of an increased respiratory rate. If a person is made to breathe rapidly and deeply for a period of from three to five minutes, his blood pressure falls. In normal persons, this fall is from 10 to 20 systolic and from 5 to 10 diastolic. In persons with hypertension, the fall is most striking. After doubling the rate of respiration for five minutes, an individual with a systolic pressure of 200 and a diastolic of 110 had

a blood pressure of only 140 systolic and 80 diastolic. When normal breathing was resumed, the pressure rose rapidly to its regular high level.

In hypertension of long standing, that is, when it occurs in older persons, this phenomenon is less marked, but in young subjects, that is, when the high blood pressure is not of long standing, the fall is most marked.

In a series of ten patients from 40 to 45 years of age with blood pressures averaging 175 systolic and 105 diastolic, the average pressure became 150 systolic and 90 diastolic after the rate and depth of respiration were doubled for five minutes.

In 100 syphilitic patients with normal blood pressure and no cardiovascular changes in clinical evidence, 75 per cent gave a respiratory rebound averaging 175 for the group, as compared with an average of 15 per cent in nonsyphilitic persons. This is certainly in accord with the conception that syphilis is first and always a vascular disease.

The mechanism of apoplexy is demonstrated by the respiratory rebound. Apoplexy that comes on as the result of excessive muscular effort does not come on during the effort but after it. During hard muscular effort, the arterial pressure falls as the blood is held back in the venous system, but when effort ceases deep respirations ensue, the venous blood is released, the heart and arteries are overdistended, the pressure rises, and apoplexy is the result. Apoplexy is often caused by straining at defecation, but it does not come on during the effort of straining but afterward. I observed a man carry his wife, who had been injured in the street, up a flight of steps into the house and lay her on a couch. It was a terrific effort, as the wife weighed 160 pounds (72.6 Kg.). After placing her on the couch, he took a few deep breaths, and had a sudden fatal stroke of apoplexy. This is the mechanism of apoplexy occurring in patients with low blood pressure and hardened arteries. Acute dilatation of the heart is thus caused on effort.

The observations here set forth were made in 1910, and were so reported to the Des Moines Medical Library Club (unpublished). At that time it was stated that the value of this test could be determined in a patient only after the lapse of many years—at least twenty. If a person with a normal pressure, as usually determined, shows a high pressure on expiratory effort indicating an inelastic condition of the arteries, time alone will tell if this inelastic condition is of clinical importance.

It was first necessary to determine what constitutes a normal and an abnormal rebound. After the test was applied to 1,000 persons, it was evident that an elevation of arterial tension not exceeding 25 was

the rule, so this was considered normal. Increases in pressure above that were found to be unusual, and were considered abnormal. It was possible to select a series of 100 persons from 40 to 45 years of age, who twenty years ago showed an abnormally high rebound. This series was checked with an equal number of persons of the same age who at the same time showed a normal rebound. At rest, the normal series had an arterial tension not exceeding 140 systolic, and a systolic rebound not exceeding 165. The abnormal series had an arterial tension when at rest not exceeding 140 systolic, with a rebound of 190 or more on expiratory effort. All of the cases were fully checked so as to exclude kidney disease and syphilis, as it was early noted that syphilitic subjects almost invariably gave an abnormally high rebound.

Of the 100 patients with a rebound to 165 or less, 88 are living and 12 died from the following causes: pneumonia, 4; acute rheumatic endocarditis, 1; nephrosis, 1; tuberculosis, 1; thrombophlebitis, 1, and myocarditis (infectious) 1; the cause of death in 3 was not determined. Of the 100 patients with a systolic rebound to 190 or more, 68 are living and 32 died from the following causes: apoplexy, 4; nephrosis, 12; angina pectoris, 4; myocarditis, 2; pneumonia, 2; influenza, 4, and dementia, 1; the cause of death in 3 was not determined.

The test has been applied to every patient with a lesion of the heart coming under observation. The series included progressive and stationary mitral lesions, acute and chronic myocarditis, rheumatic endocarditis—studied from the onset of symptoms until the fatal termination or until the lesions became stationary—lesions of the aortic valve and subacute bacterial endocarditis. In no case did the test indicate the condition of the heart as to structural changes or the degree of efficiency. While the test is seemingly a severe strain on the heart, in no case was there evidence of its being harmful. In cases of heart failure, the sense of air-hunger comes on so early in making the blowing test that it was necessary for breathing to be resumed before damage was done.

COMMENT

It has been observed that a forced expiratory effort made with the exit of air closed causes a drop in systolic pressure; that when the breathing is resumed there is a marked elevation in the pressure, and that the elevation so produced is usually not more than 25 above the individual's pressure at rest. This pressure was therefore considered normal. In some persons the pressure rises to 75 or more above the pressure at rest. Such rebounds were considered abnormal.

It was shown that the change in pressure was due to shutting off the supply of blood to the heart because of increased intrathoracic

pressure, thereby causing a drop in pressure, and that when normal respirations were begun the heart and arteries were suddenly overloaded by the blood that had been dammed back, thus causing a sudden high wave of arterial tension.

It was observed that the intrathoracic pressure never exceeded the intra-abdominal, a fact which explains the physiology of the supply of blood to the heart during effort.

It was demonstrated that an abdominal high wave of arterial pressure was due, not to the condition of the heart, but to the diminished elasticity of the arteries.

A series of 100 patients with abnormally high rebound was checked with that of an equal number with a normal rebound. These two series were kept under observation for twenty years. The mortality in the series with a high rebound was 32 per cent in twenty years compared with a mortality of 12 per cent in the series with a normal rebound. The high mortality was due to vascular or renal failure.

CONCLUSIONS

The test is a positive measure of arterial elasticity, and is of definite clinical value.

A high respiratory rebound is the first indication of oncoming hypertension and of arterial fibrosis, with or without high pressure.

A person showing a high rebound should be intensively studied for syphilis and nephritis.

The test does not indicate the integrity of the heart, measure its efficiency or foretell its failure.

THE VALUE OF DETERMINATIONS OF THE IRON CONTENT OF WHOLE BLOOD*

WILLIAM P. MURPHY, M.D.

RALPH LYNCH, M.D.

AND

ISABEL M. HOWARD

BOSTON

That iron is a constant and important constituent of the hemoglobin of mammals has been recognized for many years, and in consequence it has played an important rôle in the treatment for anemias. Therefore, it is somewhat surprising to find so little evidence in the literature of studies of the blood iron. Although a few determinations of the iron content of the blood under varying conditions have been made, there has been little effort to utilize these figures as a means of distinguishing between the various types of anemia or to follow the changes that may occur in the hemoglobin during the course of treatment for anemia by means of iron or other substances.

The observations recorded in this paper were made particularly in order to determine another means of differentiating between the types of anemia and also to establish a satisfactory method of following the changes that may occur in the blood of an anemic person being treated with various substances. With this in mind, it seemed advisable to establish the normal figure for whole blood iron by determinations on the blood of a group of normal persons. Few determinations of whole blood iron have been recorded on normal human blood in recent years which are comparable to the figures here recorded.

METHOD AND PROCEDURE

Ten cubic centimeters of blood was withdrawn from a vein of the arm and placed in a test tube that had been previously prepared by evaporating to dryness therein 2 cc. of a 1.6 per cent solution of sodium oxalate that contained no iron. Gentle tilting of the tube prevented clotting and the formation of air bubbles which occur with shaking. The amount of hemoglobin in the blood was usually estimated by Osgood and Haskins'[1] modification of Sahli's method, and a careful red blood

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* From the Medical Clinic of the Peter Bent Brigham Hospital.

* This study was aided by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Disease.

1. Osgood, E. E., and Haskins, H. D.: A New Permanent Standard for Estimation of Hemoglobin by the Acid Hematin Method, J. Biol. Chem. **57**: 107, 1923.

cell count was made, standardized pipets and counting chambers being used. Duplicate determinations were made of the iron contained in the whole blood by the colorimetric method suggested by Kennedy.[2] This method was chosen because the chemical principles involved appeared to be sound and because it is a sufficiently simple method to be of practical value in the average chemical laboratory. Kennedy pointed out that the principle advantages of this method over others that have been suggested are the use of perchloric acid as a means of digesting the blood more rapidly and the addition in like amount of all reagents both to the standard iron solution and to the "unknown" blood. In this way the reaction of both is kept the same, and any traces of iron that might be contained in the reagents used will appear in equal amounts in the standard as well as in the "unknown." It has been pointed out by Kennedy and confirmed by us that after the ferric thiocyanate color has been produced, the reading will be influenced both by heat and by delay in making the colorimetric reading. Therefore, it is necessary to maintain a fairly uniform temperature in the flask and also to prepare only a few specimens at a time for colorimetric reading. The presence of small amounts of phosphates does not affect the reading. Although it was possible to check the determinations for iron made by Kennedy's method and the iron content of normal blood was found to range within rather narrow normal limits, our observations suggested that the "normal" figures so obtained are lower than the true values. A discussion of this subject will be considered in a paper which will appear later.

The amount of iron in the whole blood is expressed in milligrams per hundred cubic centimeters of whole blood.

The Iron Index.—By dividing the milligrams of iron per hundred cubic centimeters of blood by the number of red blood cells per hundred cubic centimeters of the same venous blood used in making the determination for iron, it is possible to know the amount of iron in the average individual red blood cell and therefore to compare the relative concentration of iron in the blood of different persons. As it was believed that such a determination would be of significance in differentiating between the types of anemia, a more practical calculation is suggested which would indicate roughly the same information. It is suggested that the figure so obtained be called the "iron index," and it may be calculated by dividing the number of milligrams of iron per hundred cubic centimeters of blood by the red blood cell count expressed in millions per cubic millimeter of venous blood. For example, a person having 4,700,000 red blood cells per cubic millimeter and 41 mg. of iron per hundred cubic centimeters of venous blood would have an iron index of $\frac{41.0}{4.70}$ or 8.7. This figure (the iron index) may be used in place of the color index in differentiating the anemias, and it is probably a more reliable figure than is the color index as generally calculated.

RESULTS

Normal Persons.—It is difficult to compare the figures for whole blood iron which we have obtained with many of those that are available in the literature, owing to the fact that the earlier figures are generally recorded in terms of a given weight rather than volume of blood. The

2. Kennedy, R. P.: The Quantitative Determination of Iron in the Tissues, J. Biol. Chem. **74**:385, 1927.

methods of determining the blood iron have varied considerably, so that the same method has rarely been followed by any two observers.

Probably the first quantitative determinations of whole blood iron were made by Le Canu, Prevost and Dumas [3] in 1820. Andral and Gavarret [4] followed with some observations in 1842, as did Bequerel and Rodier [5] in 1845, and C. A. Schmidt [6] in 1850. Subsequently, several other observations were made, notable among which were those obtained by means of Jolles' ferrometer. Although the figures obtained by Le Canu and his co-workers and by Andral and Gavarret are not available,

TABLE 1.—*Observations of Early Workers on the Iron Content of Whole Blood of Normal Persons*

Author	Year of Observation	Iron Content, Mg. per 100 Cc.
Bequeral and Rodier, quoted by Fowell: Quart. J. Med. **6**: 179, 1912-1913	1845	0.0555 male 0.051 female
Schmidt, C. A.: Ibid.	1850	0.0512 male 0.0485 female
Pelouze: Ibid.	1865	0.0506 male 0.0537 female
Jarisch: Ibid.	1879	0.0506
Biernacki, E.: Ztschr. f. klin. Med. **24**: 460, 1894	1894	0.0519 male 0.0566 female
Erben, F.: Ztschr. f. klin. Med. **40**: 266, 1900	1900	0.0545
Newman, A.: Ztschr. f. physiol. Chem. **37**: 115, 1902	1902	0.0519
Mayer, A.: Ztschr. f. klin. Med. **40**: 475, 1903	1903	0.0515
Jolles: Deutsche med. Wchnschr. **24**: 104, 1898*	....	0.0486
Hladik, J.: Wien. klin. Wchnschr. **1**: 74, 1898* (average of 30 cases)	....	0.0425
Rosen, H., and Jellinek, S.: Ztschr. f. klin. Med. **39**: 109, 1900* (average of 10 cases)	....	0.0527
Jolles and Winkler: Arch. f. exper. Path. u. Pharmakol. **44**: 464, 1900*	....	0.0575

* These authors obtained their values by means of the Jolles ferrometer.

those of other of the early workers are given in table 1 in percentage by weight of whole blood.

In 1918, Berman [7] recorded the blood iron in six instances with an average of 48.6 mg. per hundred cubic centimeters of blood, but

3. Le Canu; Prevost, and Dumas, quoted by Biernacki, E.: Ztschr. f. klin. Med. **24**:460, 1894.

4. Andral and Gavarret, quoted by Meyer and Gottlieb: Pharmacology, Clinical and Experimental, trans. by John T. Halsey, Philadelphia, J. B. Lippincott Company, 1914.

5. Bequerel and Rodier, quoted by Fowell, P. H. C.: Quart. J. Med. **6**:179, 1912.

6. Schmidt, C. A., quoted by Fowell (footnote 5).

7. Berman, L.: A Rapid Method for the Determination of Iron in Small Quantities of Blood, J. Biol. Chem. **35**:231, 1918.

did not state whether or not human blood was used. In 1922, Brown [8] stated that the figure for normal blood iron varies between 45 and 52 mg. per hundred cubic centimeters, but did not state the source of his figures. In 1926, Mengert-Presser [9] quoted van den Bergh and Engelkes as having stated that the normal figure for blood iron is 45 mg. per hundred cubic centimeters of blood.

In table 2 are recorded figures representing the iron content of the whole blood. Twenty-one determinations were made on the blood of

TABLE 2.—*Observations of the Whole Blood Iron, Red Blood Cell Count, Iron Index, Cell Volume and Hemoglobin on the Blood of Eighteen Normal Young Men*

	Iron, Mg. per 100 Cc.	Red Blood Cells, Millions per C.mm.	Iron Index	Hematocrit Total Cell Volume	Individual Cell Volume $\times 10^{-12}$ Cc.	Hemoglobin, Gm. per 100 Cc.
M-1	50.00	5.77	8.7	48.40	8.5	15.73
M-2	47.60	5.98	7.9	.....	...	15.58
M-3	46.86	5.53	8.5	48.60	8.8	15.73
M-4	46.80	5.17	9.1	45.60	8.8	15.73
M-5	46.00	5.31	8.7	45.60	8.6	15.32
M-6	45.70	5.72	8.0	.....	...	17.10
M-7	45.60	5.44	8.4	.....	...	14.70
M-8	45.60	5.32	8.6	43.60	8.2	14.90
M-9	45.60	5.21	8.8	41.70	8.0	15.40
M-10	45.20	5.55	8.2	.....	...	14.52
M-11	44.80	5.47	8.3	.....	...	15.90
M-12	44.50	5.36	8.3	.....	...	14.52
M-13	44.40	5.63	7.9	.....	...	14.88
M-7A	44.12	5.19	8.5	43.54	8.4	13.52
M-14	43.80	4.87	9.0	42.09	8.6	15.20
M-15	43.50	5.47	8.0	40.00	7.3	14.77
M-16	43.40	4.78	9.0	.....	...	13.84
M-14A	43.20	5.32	8.1	.....	...	14.88
M-17	42.60	5.34	8.0	45.90	8.6	13.80
M-16A	42.40	4.84	8.8	.....	...	15.40
M-18	42.00	5.04	8.4	.....	...	14.88
Average	44.84	5.35	8.4	44.50	8.38	15.06

eighteen normal young men, the ages ranging between 20 and 40 years. It may be seen in this figure that the red blood cell counts vary between 4,780,000 and 5,980,000 cells per cubic millimeter, the average being 5,350,000. The hemoglobin varied from 13.52 to 17.1 Gm., the average being 15.06 Gm. per hundred cubic centimeters of blood. The iron content of the whole blood varied from 42 to 50 mg. of iron per hundred cubic centimeters of blood, the average being 44.84 mg. The iron index calculated from the red blood cell count and the iron content of the blood varied from 7.9 to 9.1, the average being 8.4.

8. Brown, A. L.: A New Quantitative Method for the Determination of Iron in the Blood, J. Am. Chem. Soc. **44**:423, 1922.

9. Mengert-Presser, H.: Bestimmungen von Hämoglobin und Eisen im Blut unter tropischen Verhältnissen, Mededeel. v. d. dienst d. volksgezondh. in Nederl.-Indië **3**:240, 1926.

In ten instances the individual cell volume was determined from the red blood cell count and the total cell volume calculated from the hematocrit as previously described by one of us.[10] This figure varied from 7.3×10^{-11} to 8.8×10^{-11} cc., the average being 8.38×10^{-11} cc.

In table 3 are recorded similar observations made on the blood of twenty-one normal young women also ranging in age between 20 and 40 years. In this group the red blood cell count varied from 4,440,000 to 5,470,000 cells per cubic millimeter of blood, the average being 4,920,000.

TABLE 3.—*Observations of the Whole Blood Iron, Red Blood Cell Count, Iron Index, Cell Volume and Hemoglobin on the Blood of Twenty-One Normal Young Women*

	Iron, Mg. per 100 Cc.	Red Blood Cells, Millions per C.mm.	Iron Index	Hematocrit Total Cell Volume	Individual Cell Volume $\times 10^{-11}$ Cc.	Hemoglobin, Gm. per 100 Cc.
F-1	46.86	5.14	9.1	....	...	13.80
F-2	46.40	5.11	9.0	43.6	9.1	14.63
F-3	45.45	5.47	8.3	47.7	8.8	14.63
F-4	44.80	4.72	9.5	42.6	9.0	14.21
F-5	43.60	4.99	8.7	41.8	8.3	14.63
F-6	43.20	5.35	8.1	....	...	15.20
F-7	42.76	4.84	8.8	37.9	7.8	14.00
F-8	42.33	5.21	8.1	....	...	13.25
F-9	42.24	4.57	9.2	40.3	8.8	14.21
F-10	41.80	4.83	8.7	....	...	14.70
F-11	46.40	4.91	8.5	....	...	13.66
F-12	41.60	5.08	8.2	39.7	7.8	13.80
F-13	41.20	4.57	9.0	40.2	8.8	13.66
F-14	40.55	4.91	8.3	41.7	8.5	13.25
F-15	40.55	4.80	8.5	37.3	7.8	13.25
F-16	40.50	4.44	9.1	37.4	8.4	12.56
F-17	40.00	4.63	8.7	....	...	15.40
F-18	39.99	4.64	8.6	41.9	9.0	13.52
F-19	39.45	5.00	7.9	45.2	9.0	13.25
F-20	39.33	5.20	7.6	41.8	8.1	13.29
F-21	38.80	4.96	7.8	39.6	8.0	13.25
Average	42.48	4.92	8.6	41.2	8.4	13.90

The hemoglobin varied from 12.56 to 15.4 Gm. per hundred cubic centimeters of blood, the average being 13.9 Gm. The iron content of the whole blood varied from 38.8 to 46.86 mg. per hundred cubic centimeters of blood, the average being 42.48. The iron index calculated as previously discussed varies from 7.6 to 9.5, the average being 8.6.

In this group of subjects, determinations of the individual cell volume were made as previously described in fifteen instances. This figure varied from 7.8×10^{-11} to 9.1×10^{-11} cc., the average being 8.4×10^{-11} cc.

A comparison of the tables for males and females shows that the range and the average figure in each column is slightly higher in males

10. Murphy, W. P., and Fitzhugh, G.: Blood Cell Size in Anemia: Its Value in Differential Diagnosis, Arch. Int. Med. **46**:440 (Sept.) 1930.

than in females, with the exception of the iron index in which the range is greater and the average slightly higher in the females.

Observations were made of the iron content of the blood in twenty-one persons in whom the hemoglobin level and red blood cell count were considered to be essentially normal in spite of the presence of some variation from normal in the state of health. Ten of this group had diabetes mellitus. The patients were of both sexes and of widely varying ages. In this group the hemoglobin varied between 11 and

TABLE 4.—*Observations of the Whole Blood Iron, Red Blood Cell Count, Hemoglobin and Iron Index on the Blood of Twenty-One Persons with No Fundamental Disturbance of the Blood*

	Iron, Mg. per 100 Cc.	Red Blood Cells, Millions per C.mm.	Hemoglobin, Gm. per 100 Cc.	Iron Index	Diagnosis
M-1	53.10	5.55	12.62	9.5	Migraine
F-2	50.20	6.53	16.32	7.7	Diabetes mellitus
F-3	44.00	5.60	13.24	7.9	Diabetes mellitus
F-4	43.20	5.41	15.10	8.0	No disease
F-5	43.20	4.95	14.35	8.7	Asthmatic bronchitis
M-6	43.20	4.62	16.32	9.3	Jaundice (infectious)
M-7	42.24	4.57	14.20	9.2	No disease
F-8	42.50	4.69	11.00	9.1	Diabetes mellitus
F-9	41.60	4.90	14.60	8.5	Chronic infectious arthritis
F-10	41.20	4.75	14.45	8.7	? Epilepsy
M-11	41.00	4.66	.....	8.8	Diabetes mellitus
F-12	41.00	4.63	12.70	8.8	No disease
F-13	40.00	4.75	12.90	8.6	Diabetes mellitus
M-14	40.53	4.89	13.76	8.3	Agranulocytosis
F-15	40.40	5.37	12.62	7.5	Diabetes mellitus
F-16	40.40	5.07	12.90	7.9	Diabetes mellitus
F-17	40.20	4.83	16.20	8.3	Obesity
M-18	40.00	4.85	13.76	8.2	Diabetes mellitus
M-14A	39.99	4.68	13.40	8.5	Agranulocytosis
F-19	38.50	5.91	13.95	6.5	Diabetes with complications
F-20	37.50	4.49	12.42	8.4	No disease
M-21	37.00	4.58	14.60	8.1	? Lead poisoning, acute
	41.90	5.01	13.88	8.4	

16.32 Gm. per hundred cubic centimeters of blood, the average being 13.88. The red blood cell counts varied between 4,490,000 and 6,530,000 per cubic millimeter of blood, with an average of 5,010,000. The figure for whole blood iron varied between 37 and 53.1 mg. per hundred cubic centimeters of blood, with an average of 41.9. The iron index varied between 6.5 and 9.5, with an average of 8.4

An average of the figures for whole blood iron obtained in the three normal groups which included sixty-four determinations on the blood of sixty persons gave 43.1 mg. per hundred cubic centimeters, with a range from 37 up to 53.1. In only one instance was the figure above 50 and in only eight was it below 40.

That the iron index is a rather constant figure in persons with no essential variation from normal in the blood is evident from an analysis of tables 2, 3 and 4. Of sixty-four determinations of this

figure that were made on the blood of sixty persons, 45, or 70 per cent, fell within the range of from 8 to 9. In nine instances the figure was above 9 and in ten instances below 8. The average iron index for the sixty-four determinations is 8.46.

Pernicious Anemia.—In a group of forty-one persons having unquestioned pernicious anemia, sixty-eight determinations of the whole blood iron and iron index were made. The lowest figure recorded for whole blood iron was 7.7 mg. per hundred cubic centimeters of blood in a patient with 690,000 red blood cells per cubic millimeter of blood. In each instance in this group of forty-one persons, the iron index was 10 or above if the red blood cell count was 4,000,000 per cubic millimeter or lower. The highest iron index recorded is 20.6. In five instances the disease was in a state of remission, with red blood cell counts above 4,000,000 per cubic millimeter, following treatment with liver. In three of these cases the iron index was below 10, the actual figures being 8.4, 9.1 and 9.1. In one of the five cases the red blood cell count was 4,100,000 per cubic millimeter, and the iron index was 10.5. In the last case of the five, the red blood cell count was 4,630,000 with an iron index of 11.5, the patient in this case having barely recovered from a relapse when the determination was made.

The cases of three patients which were not included with the cases of pernicious anemia because of definite complications are of interest. All of the three patients were treated with liver with the usual response. One of them who had rather marked combined systemic disease showed a drop in the red blood cell count, and blood was being lost from the gastro-intestinal tract. Roentgenograms of the gastro-intestinal tract showed a possible carcinoma of the stomach. In this case the iron index was 8.5 with a red blood cell count of 3,530,000 per cubic millimeter. The diagnosis was complicated in one instance by rather severe chronic nephritis, which was present when treatment was begun, and in another by myxedema occurring after somewhat over a year of treatment with liver. The iron index varied in the first case from 9.4 to 10.5 on three determinations and in the second from 9.2 to 10 on four determinations. In both cases the red blood cell counts varied at the time of the observations between 2,300,000 and 3,920,000 cells per cubic millimeter.

From these observations on patients with pernicious anemia, one may conclude that the iron index is high during a relapse, but approaches the normal figure during a satisfactory remission maintained by means of treatment with liver or liver extract. In patients with pernicious anemia having complications tending to produce secondary anemia, the iron index is likely to approach the normal level also, rather than to remain high as in an uncomplicated case in relapse.

In eight patients having an absence of free hydrochloric acid in the gastric contents up to two hours following an Ewald test meal, there was difficulty in making a positive diagnosis. Of these eight patients, five had an iron index which fell within the range generally found in pernicious anemia. Two of the five with a high index also showed evidence of loss of blood from the intestinal tract, one of whom had an extensive adenocarcinoma of the stomach. This patient had a definite rise in reticulocytes following the ingestion of liver extract which was started when the red blood cell count was 1,800,000 per cubic millimeter. The other three cases in which the patients had a high iron index were probably early cases of pernicious anemia in which the diagnosis was made more certain by the observation of an increased

TABLE 5.—*Figures Showing the Average Normal Values for the Whole Blood Iron in Normal Persons, in Pernicious Anemia and in Chronic "Secondary" Anemia*

Diagnosis	Number of Determinations	Average	Low	High
Normal, male	21	8.4	7.9	9.1
Normal, female	21	8.6	7.6	9.5
Normal, both sexes	22	8.4	6.5	9.5
Normal, all cases	64	8.46	6.5	9.5
Pernicious anemia	68	...	16.0	20.6
Secondary anemia	100-200	...	4.3	9.0+

iron index. In three of the eight cases the patients showed a normal iron index on two separate determinations. One of these may have been an early case of pernicious anemia; the other two probably were not. All of these patients had red blood cell counts below 4,000,000 cells per cubic millimeter.

Secondary Anemia.—A large series of determinations of the whole blood iron and of the iron index were made on the blood of persons having a secondary type of anemia. Such observations showed a low or low normal iron index figure in the chronic chlorotic type and anemias resulting from chronic loss of blood, regardless of the source of bleeding, and usually a low normal figure in anemia resulting from various chronic infections, accompanying certain types of tumors of the brain and accompanying chronic cardiac disease.

Iron index determinations made on the blood of patients shortly following an acute loss of blood show figures greater than the normal ones. The amount of increase in the figure is dependent on the acuteness and the amount of the hemorrhage, it being only slightly increased above the normal if bleeding occurred in the presence of chronic anemia.

Special Cases.—In two patients with sprue observed at a time when slight anemia was present, the iron index was in both within the range of the low normal figures.

The figure for iron index was determined on the blood of four patients with leukemia. In two instances it was high (16.8 and 10.6). The first patient had chronic lymphatic leukemia, the second aleukemic lymphatic leukemia, and both had a red blood cell count of approximately 1,000,000 cells per cubic millimeter. One of the patients with a normal figure for iron index had acute lymphatic leukemia with 1,620,000 red blood cells per cubic millimeter, whereas the second patient had chronic myeloid leukemia with a normal red blood cell count.

One patient with multiple myeloma and a red blood cell count of 2,950,000 cells per cubic millimeter had a normal iron index (8). Another patient with severe myxedema and with a normal red blood cell count but a moderate reduction in the hemoglobin had an "iron index" of 9.7.

In two patients with polycythemia the iron index figures were low (7.5 and 6.7).

Special mention may also be made of the iron index figure in six patients having anemia which developed either during pregnancy or acutely following delivery. In five of these patients the iron index was normal or low. In one patient in whom a severe anemia was present after delivery and in moderate degree before delivery, the iron index was 10.9 and 9.6 on two determinations made when the red blood cell level was, respectively, 1.43 and 1.9 millions per cubic millimeter. It remains to be seen whether or not this represents a true pernicious anemia developing during pregnancy.

In five patients having Paget's sease with anemia, two with undoubted pernicious anemia had a high iron index; the other three showed a low figure.

SUMMARY

Determinations of the iron content of the whole blood were made on the blood of a group of persons having an essentially normal hemoglobin level and red blood cell count, and the figures are herein recorded. The average iron content of the blood in normal young men is 44.84 mg. per hundred cubic centimeters of blood, in normal young women, 42.48, and in a group of sixty persons of both sexes and of varying age with an essentially normal blood, the average is 42.74.

It is suggested that a figure to be known as the "iron index" be calculated by dividing the figure for whole blood iron by the red blood cell count in millions of cells per cubic millimeter. This figure normally varies between 8 and 9, the average in this series being 8.46.

In pernicious anemia during relapse, the iron index was always found to be above 10, with a tendency to approach normal during a satisfactory remission following treatment with liver.

Except in certain unusual circumstances, the iron index was found to be normal or lower than normal in chronic secondary anemia. Only in anemia resulting from acute loss of blood and in certain of the patients with leukemia was the iron index above normal and in the range generally found in pernicious anemia.

It is suggested from the preceding observations that the iron index is of definite value in distinguishing between pernicious anemia and secondary anemia in most instances, and that the constancy of the figure for whole blood iron in persons with normal blood suggests this as a satisfactory means of following the changes which may occur in the blood during treatment for anemia.

311 Beacon Street.

PERNICIOUS ANEMIA WITH FATAL TERMINATION DURING A LIVER DIET

REPORT OF THREE CASES *

JAMES B. CAREY, M.D.
MINNEAPOLIS

It has been found that liver or liver extract used in the treatment for pernicious anemia has an effect on the blood only; it has no effect on either the achylia or the sclerosis occurring in the posterior and lateral columns of the spinal cord.

There is a tendency to interpret the favorable remissions obtained in the condition of the blood in patients with pernicious anemia treated by liver substance as having some enlightening implications concerning the etiology of the disease. It is easy to say, when these remissions are universally obtained, that some deficiency is being supplied to the patient with pernicious anemia and that therefore the condition must be a deficiency disease. One must not forget, however, that pernicious anemia, as now generally known, presents other important pathologic changes than those seen in the blood. The changes in the blood themselves are of a hemolytic character, as can always be demonstrated by the finding of end-products of such hemolysis in the skin, duodenal contents, urine and feces. The red blood cells in pernicious anemia may be subject to more rapid destruction than normal cells, because of some primary abnormality of the bone marrow, in which case the hemolysis is a secondary and consequent factor, rather than a primary one, but the anemia, after all, is of a hemolytic type. As part of the syndrome there is also achlorhydria in all cases, and subacute combined degeneration of the spinal column in many. In order, therefore, to deduce from any method of therapy an etiologic hypothesis, one should not be too dogmatic until some effect is demonstrated on the whole clinical picture, rather than on a single phase of the condition. Isaacs recently showed that "in pernicious anemia some of the symptoms of a relapse may occur even though a complete blood remission is maintained with liver treatment."

Of course, it is recognized that such relatively static structures as the gastric glands or the spinal cord could not be so easily modified as the more labile blood elements, yet a truly specific therapy should

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* From the Medical Division, the Nicollet Clinic.

modify or at least check the progress of all changes occurring in the condition under treatment. All that really happens in a patient with pernicious anemia under treatment with liver substance is that a prolonged remission in the condition of the blood is established, which continues only as long as the liver is administered; when and if the hepatic substance is discontinued, the blood relapses. This result was formerly sought by transfusions, injections of whole blood, arsenic and other stimulating agents. The very nature of the last-mentioned agents precluded their continuous use. Liver or liver extract can be used continuously, and thus provides continuous stimulation to the maturation of new cells, or protection against the hemolysis of poorly formed elements of the blood. In either case, a sufficient number of blood cells are kept in the circulation to maintain health and life.

The kidneys, muscles and stomach also contain whatever substance is necessary. In spite of this continued action or protection, however, the achylia persists, the changes in the spinal cord may progress, and the blood elements often fall to a level above which they do not improve and will recede or become fixed in a condition of chronic "torpid" anemia. Thus, patients may die of pernicious anemia even while on liver therapy.

Before the advent of liver in the treatment for pernicious anemia, patients died in any of several ways. They became the victims of some intercurrent infectious accident, just as any patient might. They died slowly or rapidly of a progressive anemia which none of the then known therapeutic procedures could check. They died as the result of the progress of the lesions of the cord to the condition which can be classed as "tabetic," i. e., with paralysis of the extremities, rectum and bladder and with trophic disturbances.

The three cases that I am presenting illustrate these three types of death in patients suffering from pernicious anemia who were taking adequate amounts of liver or liver extract up to the time of death. All of these patients were on the so-called "Minot-Murphy" diet, consisting of 8 ounces (226.7 Gm.) of liver and 8 ounces of lean, red meat, together with milk, butter and green vegetables daily, and in addition took from three to nine ampules of liver extract no. 343 daily. They died just as many patients died before liver therapy was known or used. It may be only fair to state that these are the only deaths which have occurred in my experience since the use of liver, and are probably less than the number of deaths that could have been expected if liver had not been used. The first patient died a so-called tabetic death, due to the progress of sclerosis of the spinal cord to its ultimate and fatal conclusion, with the blood remaining at a relatively high level of hemo-

globin content and red blood count; the second patient died as the result of a slowly progressive anemia, and the third died as the result of a rapidly progressive aplastic form of anemia.

REPORT OF CASES

CASE 1.—Dr. A. N. R., a dentist, aged 45, living in Minnesota, reported for examination on March 9, 1927, complaining of diarrhea and weakness of the legs. His father was living and well at the age of 70. His mother died of a cerebral hemorrhage at the age of 64. He had three brothers, all living and well.

He had always been in good health, except for an attack of appendicitis in 1913, for which an operation was performed. An acute, ruptured, gangrenous appendix was removed. In November, 1926, while on a hunting trip, he became so weak and exhausted that he had to return home. He was examined at that time and found to be "anemic." He remembered that in March, 1926, he had had a sore tongue for a few days, but attributed it to smoking. Under tonic and rest he improved until February, 1927, when he became weak after another attack of sore tongue. He was examined more thoroughly at that time, and a diagnosis of

TABLE 1.—*Blood Counts in Case 1*

	Hemoglobin, per Cent	Red Blood Cells	Color Index	White Blood Cells
4/14/27	60	3,480,000	0.89	.....
6/ 8/27	80	4,510,000	0.88	4,150
8/18/27	77	4,500,000	0.89	4,400
9/28/27	80	3,720,000	1.0	5,390
11/ 1/27	80	3,800,000	....	.....

pernicious anemia was made. Of interest in his past history is the fact that he had always been subject to intermittent and unexplained attacks of diarrhea. His hair became gray at the age of 25, and his skin had always shown splotchy, pigmented areas.

At the time of the original examination (March 9, 1927) he gave clinical evidence of posterolateral sclerosis of the spinal cord, more marked on the left side, and achlorhydria. Examination of the blood revealed: hemoglobin, 63 per cent; red blood cells, 2,800,000, and white blood cells, 3,950. Reticulocytes numbered 5.5 per cent, due, no doubt, to the fact that he had been on a liver diet since his previous examination. The Wassermann reaction of the blood was negative. The liver feeding was continued. A record of the examinations of the blood is given in table 1.

He went to California for the winter, where he continued his diet; he also took three vials of liver extract daily, occasionally increasing the amount to six or nine vials when he felt bad. He did not return for examination until June 11, 1928, at which time examination of the blood showed: hemoglobin, 40 per cent; red blood cells, 2,010,000; color index, 1.0, and white blood cells, 3,700. I did not hear from him again during the summer and in the fall he went to Florida. His wife reported that while in Florida he became a "crank" about the use of liver extract, taking nine and at times twelve vials daily in addition to including liver and beef steak in his diet almost every day. He began to show definite indications of mental deterioration. He engaged in wild schemes, jeopardized his finances and was headstrong and violent toward his family when they attempted to inter-

fere. He again reported for examination on March 13, 1929, demanding immediate transfusion because he did not feel as well as before. His hemoglobin content was 76 per cent; the red blood cells numbered 2,990,000 and the white blood cells 5,450; the color index was 1.31.

Neurologic examination revealed a marked increase in changes of the spinal cord; he himself realized this, as he had had to use a cane on account of a distinctly tabetic gait. Largely on account of his mental condition, he was placed in a hospital and kept under sedatives. In a week he became quiet but rather suspicious and fretful. He continued the use of liver extract (no. 343) six vials daily. On March 19, 1929, examination of the blood showed: hemoglobin, 68 per cent, and red blood cells, 3,500,000; on March 27, hemoglobin, 69 per cent, and red blood cells, 3,630,000.

He was kept on liver extract—usually six vials, but occasionally nine daily—but the changes in the nervous system became progressively worse. He was often disoriented and irrational. He had various obsessions and often auditory hallucinations. He became weaker and was finally bedridden because of inability to use his legs. He became incontinent as to urine and feces, and a decubitus ulcer developed over the sacrum. Until his death examinations were made only of the hemoglobin content of the blood; these showed 69 per cent on April 3, 1929, 60 per cent on April 7, 56 per cent on April 15 and 50 per cent on April 20. One of his obsessions was that he was not getting enough liver extract. He was therefore allowed to keep a few vials on his bedside table and he took some extract in plain water whenever he desired; no accurate record was kept of these extra amounts.

He died on April 22, with a terminal temperature due to an infected bladder, decubitus ulcer and bronchopneumonia.

Comment.—There can be no doubt but that death in this case was due to the changes in the spinal cord which produced the damage to the bladder and the trophic disturbances of the skin, thus allowing the entrance of systemic infection. His condition was identical with that seen in many cases in the past, in which the hemoglobin remained at about 50 per cent and the red blood cells at 2,500,000, but in which mental changes supervened and the tabetic changes progressed to death.

Case 2.—Mr. C. P. J., aged 72, a retired farmer residing in Iowa, was first seen at the Clinic in October, 1926, complaining of weakness, anorexia and insomnia.

His father died of pneumonia at the age of 63; his mother, of senility at 90. Two brothers died of pneumonia.

In 1893, he was supposed to have had a bleeding ulcer of the stomach, during which time he became pale and weak. He recovered and was well until 1911, when he had a slight stroke with double vision, from which he recovered. In 1920, he had pneumonia and in 1924, influenza. In June, 1925, he consulted Dr. Woodward of Mason City, Iowa, complaining of dyspnea on exertion, edema and pain in the legs.

Examination at that time gave negative results, except for the edema and anemia. His hemoglobin content was 58 per cent; the red blood cells numbered 1,440,000, and the white blood cells 4,200. He was given injections of arsphenamine, and his condition improved. In October, 1925, his hemoglobin content was 70 per cent; the red blood cells were 3,500,000, and the white blood cells 6,000. In January, 1926, he was somewhat worse and was given another course of arsphena-

mine. He improved again until April, when he became worse. He stated that at that time arsphenamine was of no avail. He was in the hospital for two months, with no improvement. During this time he had severe diarrhea. On his discharge, examination revealed: hemoglobin, 38 per cent, and red blood cells, 1,400,000.

When first examined, in October, 1926, he was very weak and was hospitalized immediately. We obtained the additional history of a sore mouth, supposedly due to dental plates, in the spring of 1926, and some paresthesia of the hands and feet during that summer. When first observed, his hemoglobin content was 8 per cent and the red blood cells numbered 570,000. He was very edematous. During his stay of seven weeks in the hospital he was given a transfusion once, and merbaphen was administered to eliminate the edema; he was placed on dilute hydrochloric acid and liver. He received daily from the diet kitchen at least one-half pound of liver,

TABLE 2.—*Blood Counts in Case 2 While the Patient Was in the Hospital*

	Hemoglobin, per Cent	Red Blood Cells
11/ 4/26	19	1,230,000
11/10/26	25	1,430,000
11/17/26	31	1,800,000
12/ 4/26	54	2,390,000
12/11/26	57	2,500,000
12/18/26	63	3,850,000

TABLE 3.—*Blood Counts After Patient's Discharge*

	Hemoglobin, per Cent	Red Blood Cells	Color Index
1/10/27	75	3,710,000	1.0
2/ 9/27	71	2,900,000	1.2
3/25/27	63	2,540,000	1.2
5/13/27	65	2,500,000	1.3
8/15/27	61	2,570,000	1.2
11/ 2/27	47	2,030,000	1.1

prepared in various ways, and six vials of extract no. 343 daily. His appetite was good at all times. Repeated examination showed typical symptoms of pernicious anemia: a lemon yellow skin and sclera, atrophic tongue, hemic heart murmur, edema and evidence of moderate posterolateral sclerosis of the spinal cord. Achylia was present. The Wassermann reaction of the blood was negative. On his discharge, Dec. 19, 1926, the hemoglobin content was 63 per cent and the red blood cells numbered 3,850,000.

The blood counts made at the hospital, following the transfusion and institution of liver feeding, and after the patient's discharge are given in tables 2 and 3, respectively.

During all this period he felt fairly well, but in November he complained of weakness again, and showed some edema of the ankles. He went to Florida for the winter, felt well, and did not report again until June 2, 1928, when examination revealed: hemoglobin, 52 per cent; red blood cells, 2,430,000, and color index, 1.08. He said that he had kept up a maintenance dose of from three to six vials of liver extract daily and that he ate liver and beef as often as he could obtain them. He had been out in the sun constantly, as his appearance indicated. On his return home in the spring his daughter supervised his diet and medication.

For a short period he used a liquid liver extract with which I had had no experience, but when this was discovered he was advised to abandon its use and return to the original extract, which he did.

At this time he was distinctly weaker, although no changes in the spinal cord or general condition were demonstrated. He decided that he would return to his home in Charles City, Iowa, where he thought he would be more comfortable with a daughter; he died there on Feb. 19, 1929. No definite or accurate report concerning his death was received except from relatives, who said that he gradually became weaker and died. His daughter had been instructed as to the liver diet and the proper amounts of extract. He had continued these until he became too weak to eat anything. • During his entire period under observation he took adequate amounts of either liver or liver extract daily.

Comment.—This patient died as the result of slowly progressive anemia. Undoubtedly, the blood elements were reduced to a lower level after the final readings. A possible factor in this case must have been the age of the patient. Probably even a potent stimulant like liver becomes ineffective in a man aged 74. He had certainly lived out his expectancy. Nevertheless, he died of anemia while on an adequate diet of liver.

TABLE 4.—*Subsequent Blood Counts in Case 2*

	Hemoglobin, per Cent	Red Blood Cells	Color Index
8/22/28	55	2,670,000	1.05
10/25/28	43	1,830,000	1.09
11/19/28	44	1,810,000	1.22
12/21/28	46	1,600,000	1.12

CASE 3.—Miss E. D. MacL., aged 68, was sent to the clinic for examination on May 29, 1929. She complained of weakness. Her family history was unimportant. She had had pneumonia in 1918 and some trouble with her joints for the past four years. During this period she had also had paresthesia of the hands and feet, with the "glove-sock" distribution. During the past winter she had become weak and been dyspneic on exertion. On April 19, she entered the Fifth Avenue Hospital in New York, under the care of Dr. C. F. Tenney. His report showed negative results on general physical examination, achlorhydria and, on May 4, 1929, a hemoglobin content of 19 per cent; the red blood cells numbered 1,300,000 and the white blood cells 5,200. Dr. Tenney's clinical diagnosis was pernicious anemia. She received transfusions there on May 7, 13 and 22; the record of the blood counts is given in table 5.

She was also given liver extract and dilute hydrochloric acid. Examination at the clinic on May 29, 1929, showed a marked pallor and signs of posterolateral sclerosis of the spinal cord. The blood pressure was 135 systolic and 62 diastolic. The hemoglobin content was 36 per cent; the red blood cells numbered 2,120,000 and the white blood cells 5,000. She was placed in the hospital, given six transfusions and kept on liver extract—from six to nine vials daily. She was also given liver and beef by order from the diet kitchen. A record of a few of her blood counts is given in table 6.

During her stay in the hospital she had frequent attacks of precordial pain, with dyspnea. A clinical diagnosis of severe anemia, with posterolateral sclerosis of the spinal cord and coronary sclerosis was made. She continued to receive the "liver diet" and extract no. 343 up to the time of death. For a short period she received twelve vials daily. On July 23, at 11:30 p. m., the patient became restless and tossed about in bed. Morphine failed to quiet her; she became dyspneic and died at 1:30 a. m.

An autopsy performed by Dr. A. E. Kumpf, of the Department of Pathology, the University of Minnesota, revealed: The heart weighed 400 Gm. with moderate hypertrophy of the left ventricular musculature. The valves were normal. There was marked sclerosis and calcification of both coronary arteries. The spleen weighed 225 Gm. The liver weighed 1,575 Gm. The bone marrow from the

TABLE 5.—*Blood Counts in Case 3 Before Hospitalization*

	Hemoglobin, per Cent	Red Blood Cells	White Blood Cells
5/ 8/29	32	2,100,000	.....
5/13/29	24	1,600,000	5,700
5/14/29	43	2,600,000	.....
5/18/29	41	2,800,000	5,000
5/21/29	47	1,900,000	.....
5/22/29	50	2,400,000	.....

TABLE 6.—*Blood Counts After Hospitalization*

	Hemoglobin, per Cent	Red Blood Cells	Platelets	Reticulocytes
6/ 8/29	22	1,800,000		
6/11/29	33	2,100,000	150,000	None
6/14/29	36	2,200,000		
6/18/29	20	2,500,000		
6/28/29	32	2,700,000		
7/ 1/29	28	1,850,000		
7/10/29	30	1,750,000		
7/20/29	26	1,600,000		
7/22/29	18	1,115,000		

center of the shaft of the left femur was yellow, except the part adjacent to the bone, which was dark red. Microscopically, the liver showed slight lymphocytic infiltration of the portal canals and some fatty change of the central parts of the lobules. The spleen showed some hyperplasia of the malpighian corpuscles. Both showed an increase of iron pigment with potassium ferrocyanide stain. The bone marrow showed numerous myelocytes and myeloblasts, a few eosinophils, metamyelocytes and some megakaryocytes. There were no normoblasts or megaloblasts. The spinal cord showed sclerosis in the lateral and posterior columns. The pathologic diagnosis was: (1) subacute combined degeneration of the spinal cord; (2) pernicious anemia, probably in the aplastic stage; (3) hemosiderosis in the liver and spleen; (4) moderate metaplasia of the bone marrow; (5) coronary sclerosis in cardiac hypertension, and (6) hypertension of the kidneys.

Comment.—The complication of coronary sclerosis undoubtedly had something to do with the sudden death in this patient. The observations at autopsy indicated that there was cardiac and renal disease

which undoubtedly would have eventually caused death without the concurrence of the pernicious anemia. In this patient, however, the blood did not react to the stimulation of either transfusions or liver. To meet a possible criticism, it may be mentioned that the extent of the nephritis was not thought to be sufficient to account for any degree of anemia. Neither was the heart decompensated. The liver, for instance, showed only such degenerative changes as should result from the anemia, and there was not a sufficient amount of passive congestion to account for the failure to react to stimulation.

SUMMARY

Three patients with pernicious anemia died while under treatment with adequate[1] amounts of liver or liver extracts. They died just as one might have expected before the advent of liver therapy, although, with the exception of the third patient, possibly not so rapidly. I do not wish to draw any conclusions from these few cases, but certain comments may be made. Liver therapy apparently has no effect on the ultimate outcome in every case of pernicious anemia. It is too soon to begin to be hopeful that liver substances can indefinitely check the progress of the disease. In considering the result of liver therapy with the idea of deducing an etiologic hypothesis, it must not be forgotten that achylia and sclerosis of the spinal cord are integral parts of the syndrome and that these changes are apparently unaffected by liver. In certain cases it is evident that one must expect death as the result of the progression of disease of the spinal cord, in spite of a relatively good condition of the blood. In other cases, the blood-forming organs become incapable of further regenerative effort, perhaps as the result of the age of the patient, or even conceivably in younger patients because of exhaustive overstimulation. Finally, there are patients with an aplastic marrow who cannot become stimulated initially.

1. By "adequate" is meant an amount, found in other patients so treated, that will keep the blood count and hemoglobin percentage up to reasonable normal levels; usually to obtain an initial response, nine vials have been used daily, and to maintain the level, from three to six vials daily depending on the amount of liver the patients were eating. All the patients observed were maintained on a modified "Murphy-Minot" diet, as described in connection with the first case.

1009 Nicollet Avenue.

TUBERCULOUS INFECTION

ATTEMPTS TO PREVENT IT BY SUBCUTANEOUS VACCINATION WITH B C G*

JOHANNES HEIMBECK

OSLO, NORWAY

The basis of all work on tuberculosis is the knowledge of tuberculous infection, and when the question of combating the disease by means of prophylactic vaccination arises the conditions influencing the infection become of vital importance. An account of tuberculous infection will therefore be given, with the observations on which vaccination is based, followed by a description of subcutaneous vaccination with B C G and its results.

The common conception of tuberculous infection is that it generally occurs during the early years of childhood. The many difficulties that continually arise, however, when an attempt is made to bring actual facts concerning tuberculosis into line with this theory, for instance, the morbidity at the ages between 20 and 30 years, make one doubt the truth of the theory. And the facts on which the theory is based do not seem convincing; they are too few and too specialized to justify such a general hypothesis regarding infection in childhood. For this reason, the question of tuberculous infection was made the subject of further investigation, and the results are published in the present communication.

The work has been proceeding since 1926, and covers the three social classes which constitute practically the whole population of Norway, as of other countries, namely, the country dwellers and the two classes of townsfolk, the middle class and the workers. The subjects were of all ages, the investigations being made on a large scale among the ordinary, presumably healthy population. The method of investigation was Pirquet's cutaneous tuberculin test, as well as an ordinary clinical and roentgenologic examination in special cases.

The Pirquet test was chosen for the following reasons: 1. If not an absolutely infallible test of tuberculous infection, it is so reliable that the percentage of error in mass investigations is negligible; e. g., of 50 persons under 21 years of age giving negative Pirquet reactions not one gave a positive Mantoux reaction with 1 mg. of tuberculin. 2. It is the easiest and quickest method for the investigator, and in the way that it was used in this investigation it is the least trying to

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the subjects being tested. After personal experience with from 5,000 to 6,000 tests, the following is the method that I now use: The skin of the upper part of the left arm is washed with ether, and 2 transverse stripes of concentrated old tuberculin (equal parts of human and bovine) 2 cm. long, are put on, 5 cm. apart. Then the epidermis is cut with a lancet through the stripes of tuberculin, and the arm is left uncovered for ten minutes before the clothes are again put on, to allow the tuberculin to dry. It should be noted that a lancet and not a perforator is used. The perforator often causes a mechanical action which can easily be, and undoubtedly often is, mistaken for a tuberculin reaction. It should also be noted that the control incision is omitted. It was found to be unnecessary in the first 3,000 or more investigations.

The reaction is judged after forty-eight hours. If there is an area of 5 mm. or more of redness and infiltration along the tuberculin incisions, the reaction is positive and the test finished. If the reaction is less or is entirely absent, the test is repeated and again judged after forty-eight hours. If it is then positive, the two first tests will usually be strengthened and the reaction in the second test will be more vigorous. Some personal experience is necessary, however, in judging the weaker reactions, which are seen especially with increasing age. In most cases, however, the positive reaction is so marked, particularly in children, that there is no doubt about it. In children less than 15 years of age the reaction at the first test is so reliable that a second one is unnecessary in mass investigations, as only 0.8 per cent of the children giving a negative reaction at the first test give a positive one at the second (878 cases).

These technical details have been described minutely because the value of an investigation depends on the accuracy of the technic. I shall now pass on to the investigations and their results.

RESULTS OF INVESTIGATION

For purposes of presentation it is easiest to begin with the two classes of town dwellers. These investigations were carried out in Oslo, the capital of Norway, a seaport and industrial town of about a quarter of a million inhabitants. Altogether 3,743 persons—2,188 of the working class and 1,555 of the middle class—were examined. They were arranged in three year groups, the first group from birth to 3 years of age, the second group from 4 to 6 years, and so on, until the age of 30; then in ten year groups up to the age of 50, and, finally, all above this age in one group. The results are shown in figure 1, which gives the percentage of those giving positive Pirquet reactions in each group.

In persons of the working class the following results were obtained: Ten per cent of the first group gave a positive reaction, that is, were

infected with tuberculosis, as were 22 per cent of the second group, from 4 to 6 years of age, and 23 per cent of the next group, up to 9 years of age; then there began a more rapid increase in the number of infected persons to 38 per cent in the following three year period, reaching 50 per cent in the next group; from 22 to 24 years, there was a steady rise to 85 per cent, and from 28 and 30 years to 98 per cent, while from 40 to 50 years of age all subjects, or 100 per cent, were infected. Thus even among the working class, most of whom lived crowded together in large tenement houses, only the minority were infected with tuberculosis in childhood.

The infection occurred even later in the middle class. Here only 7 per cent of the children up to 3 years of age were infected, and

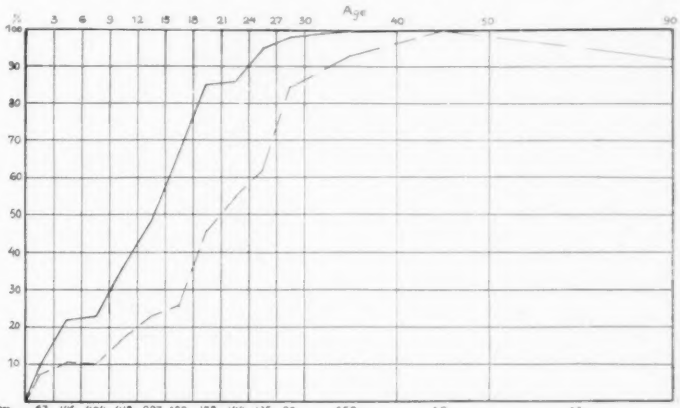

Fig. 1.—Percentage of tuberculous infection among working class (solid line) (2,188 persons examined) and middle class (broken line) (1,555 persons examined).

the percentage rose slowly during the subsequent age periods until the age of 18, when 26 per cent were found to give positive reactions. After this age, however, there was a sharp rise, so that the number of infected persons reached 84 per cent in the course of the following 12 years; then the rise continued more slowly until the age of 40 to 50 years, when every person examined was infected.

From these Pirquet curves one can draw the following conclusion, which is particularly well brought out by the curve for the middle class: In childhood only a small number are infected with tuberculosis, and the percentage increases slowly during this period of life, as the children, as a rule, are kept at home. When they are infected at this age it is

usually because there are cases of tuberculosis in the home. Therefore the first period of infection is usually in the home during childhood. Then, with the transition to a working life with its unlimited intercourse with other people and the many chances of infection outside the home, the second and great period of infection begins. It is in this period of youth, the working years, that the majority of people, and all who have escaped the infection during childhood, become infected. Owing to the different social conditions, this period starts earlier and is less marked in the working class than in the middle class.

The fact that a small number of persons are infected during childhood and the majority later in life is naturally also met with among

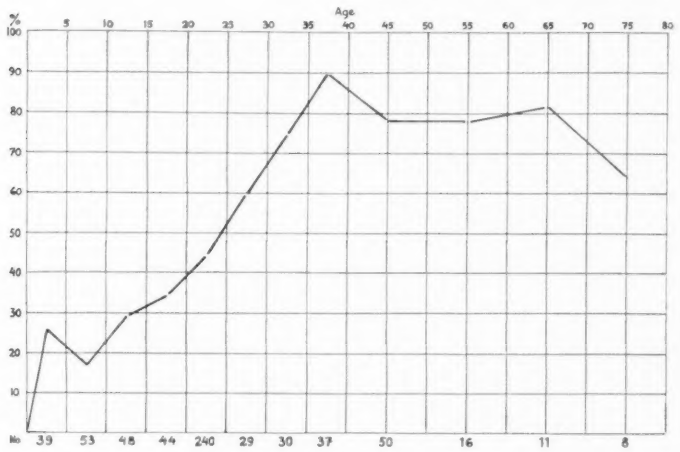

Fig. 2.—Percentage of tuberculous infection among persons in country districts. Scale at bottom of chart gives number of persons examined.

the unmixed country population, as is evident from figure 2, which shows the results by five year age groups. But among these people, whose life passes uneventfully and in the same surroundings from cradle to grave, the curve of infection runs smoothly, and by no means all persons become infected.

The foregoing conclusions can be drawn from ordinary investigations with the Pirquet reaction. I shall now consider how far they are confirmed by more specialized investigations.

I shall first deal with infection during childhood, in which a marked difference between the two town classes was shown by an investigation of school children. This is indicated in figure 3, which shows the results of the Pirquet test (*a*) in the school in Oslo which contains pupils

from the most typical and poorest working class district of the town, and (*b*) in the school composed of children from the most prosperous class of the town. The percentage is given for each year class, and it will be noticed that it rises slowly for both groups, although more rapidly for children of the working class than for those of the middle class; also that the infection is twice as common among the former children as among the latter.

The relationship between the curves indicating infection and those indicating morbidity for Oslo is shown in figure 4. The newly recorded cases of tuberculosis for one year are arranged in five year age groups

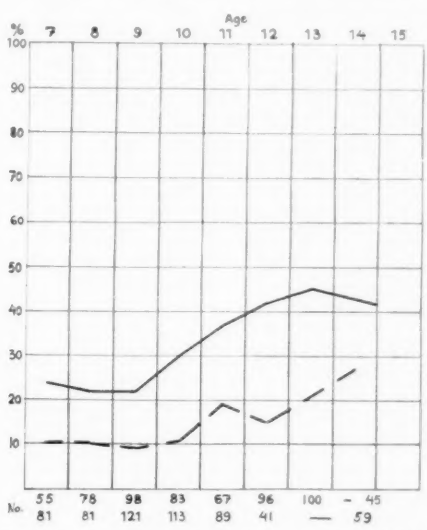

Fig. 3.—Percentage of tuberculous infection among school children of the working class (solid line) and of the middle class (broken line). Figures below chart indicate the number of children of the working class (upper row) and middle class (lower row) examined.

and are placed in columns. The morbidity was slight during the few cases of infection during childhood, whereas it was widespread during the young adult period, corresponding to the time when the second—the great—period of infection occurred. Then the number of new cases gradually fell again to zero. The morbidity curve, therefore, confirms the suggested theory of infection and seems to support the view that tuberculous disease is a direct result of the primary tuberculous infection. This question and the significance of the positive and negative Pirquet reactions will be dealt with more fully in the following account of the investigations of tuberculosis among the nurses in Ullevål hospital.

TUBERCULOUS INFECTION IN NURSES

Ullevål hospital is the municipal hospital containing about 1,500 beds, of which approximately 300 are for tuberculous cases. The latter are chiefly advanced cases of pulmonary tuberculosis in the special tuberculous wards in the 3 medical departments; they include also, for various reasons, cases in the other departments of the hospital. It is therefore easy to understand that there is ample opportunity for the nurses to become infected. These nurses are principally probationers in the nursing school of the hospital, the course of which lasts three years; it admits about 110 new probationers every year. All the nurses reside in the hospital and therefore live under similar conditions. These conditions are ideal for the exact study of tuberculous infection with, on the one hand, uniform material consisting of healthy persons of the same age—nurses in training—and, on the other hand, a constant and plentiful supply of sources of infection, with a period of three years for most careful observation.

The investigations were begun in 1924 on the initiative of my former chief, Dr. Olaf Scheel. The plan at first was to obtain Pirquet reactions from the newly admitted probationers and to keep them under observation. By degrees, however, the results made it necessary to extend the work to include the aforementioned investigations and other points.

The observations on each group are recorded separately (fig. 4) for 1924, 1925, 1926, etc. The results for the first three years are given in two columns: one for persons giving positive reactions to the Pirquet test and the other for those giving a negative reaction; for the present I am concerned with these only.

The first result, which at the time seemed curious, was that only one half of these women, 21 years of age, two thirds of whom came from the towns and one third from the country, gave a positive Pirquet reaction, that is, were infected with tubercle bacilli, a fact confirmed year after year. This has now been accounted for by the investigations referred to.

The second result, which gradually became apparent from observation of the nurses, was the overwhelming morbidity of tuberculosis among those who first gave a negative Pirquet reaction and the slight morbidity among those who had a positive Pirquet reaction to start with. This is shown in the columns of figure 5, in which each transverse stroke indicates a case of tuberculous disease. Among the probationers of 1924, 17 of the 51 who started with a negative Pirquet reaction eventually contracted the disease, while there was only 1 case among the 58 starting with a positive reaction. In the class of 1925, there were 21 cases among the 72 giving a negative reaction and 1 case among the 42 giving a positive reaction; in the class of 1926, 15 cases occurred among the 62 with an initial negative reaction and 1 case among the 52 with a positive reaction.

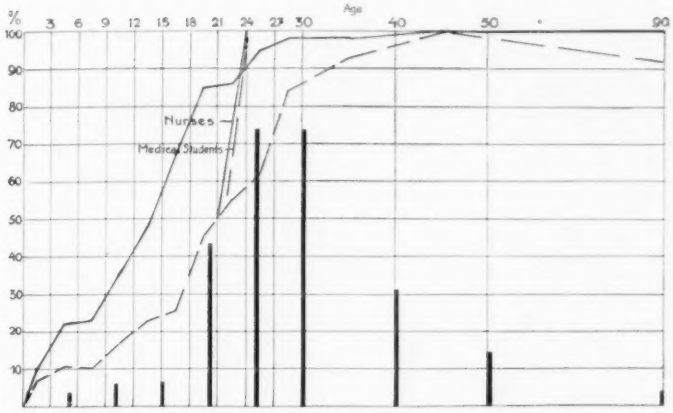

Fig. 4.—Relation between infection and morbidity curves. Solid line represents working class; broken line, middle class (infection curves for medical students and nurses are indicated); columns, newly reported cases of tuberculosis for one year, arranged in five year age groups.

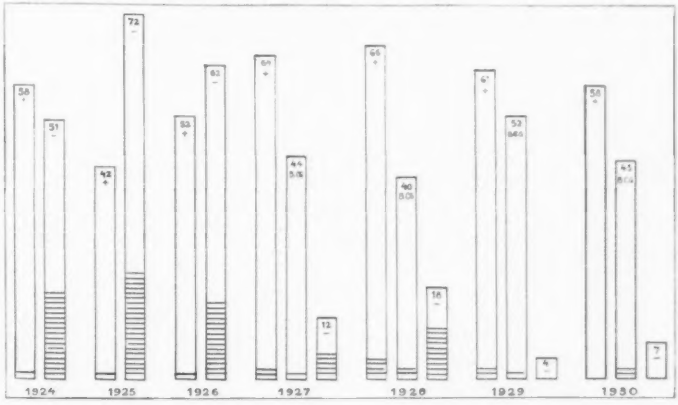

Fig. 5.—Tuberculous diseases among nurses. The columns marked with a positive sign indicate the group giving a positive reaction at the initial examination; the columns marked with a negative sign, the group originally giving a negative reaction. The other columns indicate the number of persons vaccinated with B C G. The transverse lines in the columns indicate the number of cases of tuberculous disease that developed.

It should be noted that all these nurses were thoroughly examined when they started work at the hospital and were found to be healthy. They had never had any serious illness or presented any symptoms of disease. In this respect they were all alike. They differed from each other, however, as to their Pirquet reaction. Those giving a positive reaction were infected with tubercle bacilli, but as no symptoms of the disease had been or were present the infection must have been benign. The nurses giving a negative reaction were free from tuberculous infection.

The generally accepted opinion that the presence of tuberculosis in persons between 20 and 30 years depends on a latent infection in childhood would lead one to expect that cases of tuberculosis in adults would be found mostly among those who previously gave a positive Pirquet reaction. But this is not so. On the contrary, these persons seldom become ill with the disease. It is among those who, fortunately or unfortunately, have passed through childhood and the first years of youth without contracting a benign tuberculous infection that one finds an appalling morbidity from tuberculosis when they are exposed to infection. How enormous this infection is in the hospital, was further demonstrated by the Pirquet reactions of the nurses during their training, which showed that in the course of their three years' stay at the hospital all, or 100 per cent, become infected. This is shown in figure 4, in which the nurses' curve (unbroken short line) is plotted along with that of the rest of the middle class. The extension of tuberculous infection from 50 to 100 per cent of infected cases, which takes about twenty years in the middle class, under ordinary conditions of infection, occurs among the nurses in the course of only three years, owing to the particularly favorable and abundant chances for infection in the hospital.

That the exogenous bacillary infection, in this case occurring in the hospital, is really the determining factor, is confirmed by investigations carried out on medical students. It was found that 56 per cent of the students gave a positive Pirquet reaction before they began their clinical work at the hospital, but after two years of hospital work there were 98 per cent of positive cases (fig. 4, broken short line). This group, the only one exposed to practically the same infection as the nurses were, thus had the same type of infection curve, which was distinct from that of the middle class. Moreover, it showed a remarkably high tuberculosis morbidity, for 19 of the 339 students engaged in clinical work were found to have tuberculous disease.

It is convenient at this point to examine the tuberculous disease among the nurses more in detail, especially because they afford particular information about the relation between tuberculous infection and the disease.

The tuberculous diseases in all the year groups are taken together and specified here:

Pulmonary infiltration (21 cases: 7 with, and 14 without demonstrated tubercle bacilli)
Erythema nodosum, pulmonary infiltration (16 cases: 1 with, and 15 without demonstrated tubercle bacilli)
Erythema nodosum, pleurisy (4 cases)
Erythema nodosum, pleurisy and peritonitis (1 case)
Erythema nodosum (16 cases)
Pleurisy (15 cases)
Pleurisy, pulmonary infiltration (6 cases)
Pleurisy, coxitis (1 case)
Caries of the ribs, pulmonary infiltration (1 case)

There were 81 cases in all, 10 being among the 372 nurses originally giving a positive Pirquet reaction, and 71 being among those first giving a negative reaction.

The time when symptoms of tuberculosis were noted in nurses originally giving a negative reaction gives definite information as to the interval of time between infection and the appearance of the disease. During the first six months after training began there were thirty-one cases; during the second six months, sixteen cases; during the whole of the second year, eighteen cases, and after the second year, six cases. As one can date the first chance of infection from the day that training started, though no doubt it actually occurred later when the nurses came to work in the tuberculosis wards, it can be concluded that there is not a long latent period between the infection and the outbreak of the disease, but that the infection soon betrays its malignancy. This is clear from the following observations in an individual case.

Probationer Randi began her training at the hospital on Jan. 2, 1928. She then had a negative Pirquet reaction. On February 4, a roentgenogram was taken of her lungs, as was done at that time in the case of all the nurses who originally gave a negative Pirquet reaction. As shown in figure 6, it was normal. She did not nurse tuberculous patients during the first six months, and on July 18 she still had a negative Pirquet reaction. In September she started work in one of the tuberculosis departments, and in October she no longer felt well. On October 27, another Pirquet reaction was therefore obtained and a roentgenogram taken. The Pirquet reaction then was a maximum positive one. The roentgenogram (fig. 7) showed that external to the right hilus there was an infiltrated area, about the size of a hen's egg, merging into a diffuse hilar condensation. The next day (October 28), an eruption of erythema nodosum appeared, and she became feverish. A week later, on November 5, the temperature became more irregular with a tendency to rise. On November 8, there was another outbreak of erythema nodosum. A roentgenogram (fig. 8), taken on November 9, showed a distinct enlargement of the previously observed primary infiltration—the German "Frühin-

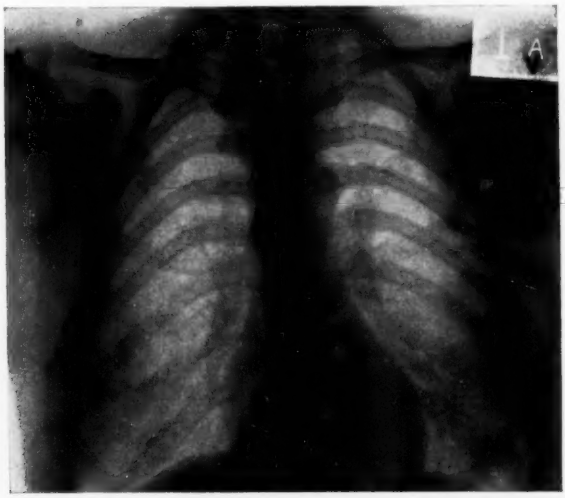

Fig. 6.—Initial (normal) roentgenogram taken on Feb. 4, 1928, in case reported.

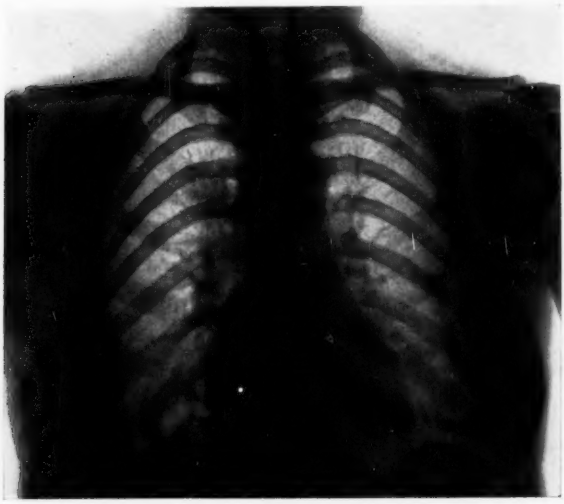

Fig. 7.—Roentgenogram taken on October 27.

filtrat"—and scattered spots spreading downward over the field of the right lung. Barely two months had elapsed from the date of the probable infection to the onset of the disease.

It only remains to draw conclusions from the fate of the nurses who started with a positive Pirquet reaction. When exposed to the identical infection which caused such a great morbidity from tuberculosis among those who started with a negative reaction, these nurses exhibited a minimum morbidity. As already stated, all that distinguished the two groups from one another was the fact that the group giving a positive Pirquet reaction already had a benign tuberculous infection when

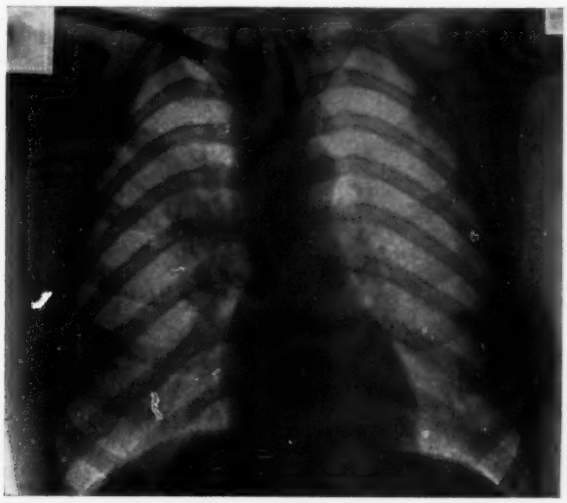

Fig. 8.—Roentgenogram taken on November 9.

exposed to infection at the hospital. Their resistance against the infection in the hospital can be attributed only to their previous infection, which must have produced immunity against a new tuberculous infection, an immunity here revealed by the Pirquet reaction. This, moreover, is merely a confirmation of Koch and Römer's demonstration of the immunity against reinfection of an animal infected with tuberculosis.

As the Pirquet reaction was, therefore, a sign of immunity against a new infection, it at once occurred to me that the natural infection —in which chance decides whether it shall be benign or malignant— might be replaced by an artificial, benign infection which, like the natural one, manifests its immunizing effect in a positive Pirquet reaction. For the production of such an infection it should be possible, theoret-

ically, at any rate, to use B C G, because it differs from the tubercle bacillus only in that it cannot be virulent. Moreover, the use of B C G in cases showing a negative Pirquet reaction would logically conform to Calmette and Guérin's rule for employing it in new-born children threatened with tuberculosis. For, like these, persons giving a negative Pirquet reaction are not infected with tuberculosis, but are extremely susceptible to tuberculosis. The scope of its application has merely been extended from infancy to adult life in conformity with the new theory of tuberculosis expounded here.

However, it would be necessary to modify the method of vaccination, as oral administration in infants is conditional on the permeability of the intestine, which soon disappears. The vaccination must therefore be done by some parenteral route. It was decided to make the injection superficially under the skin. This was done (1) because the cutaneous and subcutaneous tissues are supposed to be the chief sites for the production of antibody, and therefore give the vaccine the best chance of exerting an immunizing effect, and (2) because it was possible to watch the local action of the vaccine and to intervene if necessary.

VACCINATION WITH B C G

On the basis of this reasoning, on the one hand, and with the threat of an enormous morbidity from tuberculosis among the nurses with a negative Pirquet reaction, on the other hand, subcutaneous vaccination with B C G was tried.

It will not be necessary to describe the development of the investigation in detail. I shall mention only the essential points.

The first experiment was carried out in May, 1926, with an arbitrarily chosen dose of 0.2 mg. of B C G, suspended in a physiologic solution of sodium chloride. The result was that barely a month later the Pirquet reaction became positive. As the first step, to produce a sign of immunity, was thus achieved, the investigation was continued. As a cold abscess developed at the site of the injection in both of the first two persons vaccinated, the dose was decreased in subsequent attempts, without, however, dropping below the minimum effective dose. Since then the dose has been reduced to 0.03 and 0.02 mg., but the production of abscesses has not entirely ceased. They have become much rarer, however, appearing in only from 2 to 3 per cent of the persons vaccinated, whereas they occurred in 10 per cent when the large doses were given.

The abscess, which is the only objection to the method, is in every respect a typical cold abscess, and, like the latter, it may persist for a fairly long time. Abscesses of this kind have lasted as long as four months, depending on the treatment and their size. They have never

interfered with the subject's work, however, and have never caused any symptoms except strictly local ones, not even disease of the local glands.

I shall now consider the effect of the vaccinations which, after the orienting experiments in 1926, have been carried out systematically since January, 1927, among the nurses at Ullevål Hospital and also among the general population of Norway.

In view of the accurate data accumulated concerning infection and the observations referred to, the vaccinations of the nurses have a special interest. Immediately after they started their training and as soon as the Pirquet reaction was ascertained, the nurses who wished it were vaccinated. It was done with a suspension of 0.1 mg. of B C G per cubic centimeter, as it was thus easy to measure the dose; the injection was made by the superficial subcutaneous method. After vaccination the nurses were kept away from all patients with tuberculosis for about six weeks, which is the time that usually passes before the Pirquet reaction becomes positive, and which is therefore presumed to be the interval that must elapse between vaccination and the development of immunity. To obtain precisely comparable material, the unvaccinated nurses giving a negative Pirquet reaction were isolated in the same way. Afterward they were all free to take up the nursing of tuberculous patients.

Up to the present, 160 nurses have been vaccinated, as shown in figure 5, in which the results for each year are recorded separately. The first year was 1927, when 110 probationers began training; 64 of these gave a positive Pirquet reaction—that is, they were immune to tuberculous infection—and 56 gave a negative reaction and were therefore susceptible to tuberculosis. Vaccination was done on 44 of those giving a negative reaction, 12 of the group refusing it. After three years' training, there was only 1 case of illness (pleurisy) among the 44 vaccinated subjects, but 5 of the 12 nurses who refused vaccination had contracted tuberculosis. As in previous years, there was little morbidity among the nurses who originally gave a positive Pirquet reaction. The same holds for the year 1928, only 2 of the 40 vaccinated nurses being ill, both with pleurisy, while of the 18 nurses who were not vaccinated some form of tuberculosis developed in 10. The resistance against tuberculosis of those vaccinated with B C G is also evident for the year 1929, as when last observed none of the 52 nurses who were vaccinated in that year had devoloped tuberculosis; the same applies also to the 24 nurses who were vaccinated in January, 1930. These two periods correspond to the first year and the first six months of training, respectively, periods when, as already pointed out, most of the cases of tuberculosis occur.

The results, then, show that since 1927 there have been 3 cases of tuberculous disease among the 160 vaccinated nurses against 15 among the 35 unvaccinated nurses, and it seems clear that vaccination is effective. This view was corroborated by the Danish statistician, Professor Harald Westergaard, president of the Statistical Commission of the League of Nations, who elaborated the results up to Dec. 31, 1929. In calculating the morbidity of tuberculosis among the nurses on the basis of the actual, constant number of those in training, he found a morbidity of 4.08 per cent among those with a positive Pirquet reaction, of 33.55 per cent among those with a negative reaction and of 2.49 per cent among the vaccinated nurses. Finding that the probable mean error was only one seventh of the actual difference between the two last named groups, he declared it highly probable that the vaccination causes an effective immunity against tuberculosis.

This is also supported by the 2,000 to 3,000 vaccinations carried out simultaneously partly in Oslo and partly in different country districts in Norway. The conditions influencing infection and control are so uncertain, however, that the results are not trustworthy after such a short time, and they will, therefore, not be discussed further here.

I have dealt with the chief factor in vaccination with B C G, namely its immunizing action. Other observations made during the experiments are of less importance. A few of them, however, have some interest, both practical and theoretical, and will therefore be referred to.

First, there is the local effect of the injection of vaccine. In most cases there is none, either immediate or delayed, but for a few days after the vaccination a slight redness may appear at the site of the injection, which may be followed by infiltration. Thus infiltration was seen in twenty-seven of the nurses. It may develop at any time from the second week to the second month after vaccination, and varies in size from that of a grain to that of a pigeon's egg. It has been observed to last for as long as twelve months. In some cases the infiltrations suppurated, and in four cases the suppuration led to perforation. It is not clear from the material what causes the infiltration and possible abscess formation; for, as already pointed out, although they were more frequent in connection with the large doses of vaccine, they occurred at random following the small doses. Idiosyncrasy seems to play a part. Another point to be noted is the Pirquet reaction in the vaccinated persons.

The basis of all these vaccinations was that a subcutaneous injection of B C G called forth the power of reacting to the Pirquet test—an indication of immunity—in persons previously free from tuberculosis. This reasoning, however, proved not to be sound, for even with the larger doses and in cases in which the vaccination caused local infiltration the reaction did not always develop. With the smaller doses,

0.02 and 0.03 mg., barely one half of the subjects gave a positive reaction in the first six weeks to two months. But even when the Pirquet reaction did not become positive the vaccination seemed to produce immunity, a point of the greatest importance though antagonistic to the working hypothesis. None of the twenty-seven nurses vaccinated during the first three years—six in 1926, seven in 1928 and fourteen in 1929—who gave a negative reaction in response to the vaccination contracted the disease when exposed to tuberculous infection. It seems that these also must have become immunized. This form of immunity, however, could not have been an absolute immunity protecting against all infection, because when these twenty-seven nurses were subsequently exposed to infection they gave a positive reaction, undoubtedly due to an exogenous tuberculous infection; for in other vaccinated persons outside the hospital, some of whom have been living in surroundings free from tuberculosis since their vaccination, it is not rare to find a continued negative reaction. The effect of the vaccination seems, therefore, to be that the B C G infection tends to produce a moderate immunity before the appearance of allergy, manifested in the positive Pirquet reaction. This immunity is not strong enough, however, to prevent tuberculous infection, but it prevents the infection from becoming malignant and renders it benign, so that it acts like a new dose of vaccine increasing the production of antibody to a point where it gives an allergic reaction. In harmony, perhaps, with the fact that the B C G immunity only mitigates the effect of subsequent infections is the observation that the positive Pirquet reaction of the vaccinated nurses in tuberculous surroundings remained constant, with one exception, throughout the whole period of observation, but was found to become weaker and disappear in from one to three years in surroundings free from tuberculosis.

CONCLUSIONS

Tuberculous infection occurs in the minority of persons during childhood (the first period of infection) and in the majority during adult life (the second period of infection).

Tuberculous diseases are generally the direct result of a newly acquired infection. An infection that does not presently reveal its malignancy with symptoms of disease but merely causes allergy will seldom give rise to disease processes later; on the contrary, it protects the organism against any new exogenous infection. Pirquet's tuberculin reaction in a healthy person is therefore to be regarded as a sign of immunity. Subcutaneous vaccination with B C G is harmless and, as a rule, produces immunity, often associated with allergy. The immunity is equivalent to a benign tuberculous infection, but is probably not per-

manent. As within a certain time, perhaps from one to four years after the vaccination, it seems to be strengthened and stabilized by any later tuberculous infection, those vaccinated possibly ought to be infected with tubercle bacilli or revaccinated with B C G the first year or two after vaccination. In persons living in tuberculous surroundings and giving a negative Pirquet reaction, subcutaneous vaccination with B C G is the sovereign means of preventing tuberculosis.

PRIMARY CARCINOMA OF THE DUODENUM

REPORT OF FOUR CASES, WITH A REVIEW OF THE LITERATURE *

JACOB MEYER, M.D.
AND
DAVID H. ROSENBERG, M.D.
CHICAGO

The first report of a case of primary carcinoma of the duodenum is found among the writings of Georginis Hamberger [1] as early as 1746. In 1761, the letters of Giovanni Morgagni [2] brought to light the clinical pathologic report of the second instance, in which the condition was localized in the first portion of the duodenum. This case was said to have been encountered no later than 1733. Almost a century elapsed before additional instances were recorded. It is noteworthy that among the records and memoirs of Richard Bright [3] no reference to this condition is found. Following Chomel's [4] paper in 1852, and that of Caillet [5] in 1876, many other reports appeared. Additional instances have continued to appear in the literature.

The present report deals with four cases of primary carcinoma of the duodenum that were observed clinically and diagnosed by a careful study of the microscopic specimens. We have also made a review of the literature. It is our purpose in this article not only to report these cases, but to call attention to the need of careful, critical study and analysis of obstructive duodenal lesions.

REPORT OF CASES

CASE 1.—*History.*—A. P., a white man, aged 45, married, was admitted to the Michael Reese Hospital on June 24, 1929, complaining of jaundice, weakness, loss of weight and itching of the skin. About two months previously, he had been informed that his face was yellow. The jaundice had become progressively deeper,

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* From the Medical Service and Stomach Study Group of Michael Reese Hospital and the Medical Service of the Cook County Hospital.

1. Hamberger, G. E.: De ruptura intestini duodeni, Jena, 1746; Disputationes ad Historiam et Curationes Morborum, Albertus Hallerus, 1757, vol. 3, p. 507.

2. Morgagni, G. B.: De sedibus et causis morborum, Naples, 1761.

3. Bright, Richard: Cases and Observations on Diseases of the Pancreas and Duodenum, Tr. Med.-Chir. Soc., London **18**:1, 1832; Abdominal Tumors and Intumescence, London, The New Sydenham Society, 1860.

4. Chomel: Cancer du duodénum, Gaz. d. hôp. **10**:37 (Jan. 24) 1852.

5. Caillet: De quelques cas d'ictère mécanique dus au cancer de la deuxième portion du duodénum, Thèse de Paris, 1876.

and in the past month it had been accompanied by itching. The urine had become dark. Occasionally, a light-colored stool had been passed. During this period, the patient had lost 45 pounds (20.4 Kg.) and had become weak. The appetite had remained good. Nausea, vomiting, abdominal distress, constipation and diarrhea had not been noted.

The past history was not significant. The patient said that he had not had a syphilitic infection.

Examination.—The patient was well developed, somewhat emaciated and intensely jaundiced. The pupils were unequal; they did not react to light but did react in accommodation. The liver was enlarged, the edge being felt from 4 to 5 cm. below the costal margin. It was smooth and firm; the edge was sharp and not tender. An enlarged, tense gallbladder could be felt. The patellar and achilles reflexes were absent.

Urinalysis showed a dark amber urine with a specific gravity of 1.020. The urine was acid, and showed a faint trace of albumin; sugar, 4+; bile, 4+, and a few granular casts. The stool was clay-colored and soft, and it contained no bile, blood or fat.

Examination of the blood showed: hemoglobin, 65 per cent; red cells, 3,430,000 per cubic millimeter; white cells, 8,300; differential count: polymorphonuclears, 78 per cent; small lymphocytes, 18 per cent; large lymphocytes, 4 per cent; sugar, 250 Gm. per hundred cubic centimeters; nonprotein nitrogen, 29; icteric index, 200; the van den Bergh reaction, direct and indirect, very strong immediate positive.

An Ewald test meal was given. The stomach contents showed: free hydrochloric acid, 34; total acidity, 56; lactic acid, 0; no blood. The total amount of stomach contents obtained by the tube was 125 cc.

Examination of the spinal fluid showed: color, transparent, yellow; pressure, normal; lymphocytes, 12 per cubic millimeter; globulin, 1 plus; Lange colloidal gold curve, 0123320000; Wassermann reaction, 4+.

Roentgen examination (reported by Dr. R. Arens) showed a defective bulbus duodeni. There was a suggestion of a defect in pressure in the duodenal region, but the observations were not positive. The primary roentgenograms showed a large, well defined shadow of the gallbladder.

Course.—A low grade afternoon fever was present throughout the patient's stay in the hospital. Two weeks after admission, potassium iodide and mercurial rubs were instituted as a therapeutic test, on the supposition that we might be dealing with a syphilitic cirrhosis. Shortly after this treatment, the stools became dark and contained occult and fresh blood. The patient commenced to vomit coffee-ground material. He complained of dizziness. The jaundice was becoming less intense, and the icteric index (132) was lower than at the time of admission. The gallbladder was less prominent and not as tense. On the evening of July 10, he vomited 16 ounces of coffee-ground material containing a large clot of blood. Examination of the blood showed 1,200,000 erythrocytes per cubic millimeter and 35 per cent hemoglobin. The patient expired ten hours later.

Diagnosis.—The final diagnosis was: carcinoma of the head of the pancreas with extension to the liver, duodenum and pylorus, erosion of a blood vessel and questionable tabes dorsalis.

Necropsy.—Necropsy was performed by Dr. O. Saphir.

Gross Observation: Gross examination showed that the stomach contained a large amount of partly clotted and partly liquid blood. The duodenum showed a grayish, ragged, irregular, annular tumor. The tumor extended throughout the

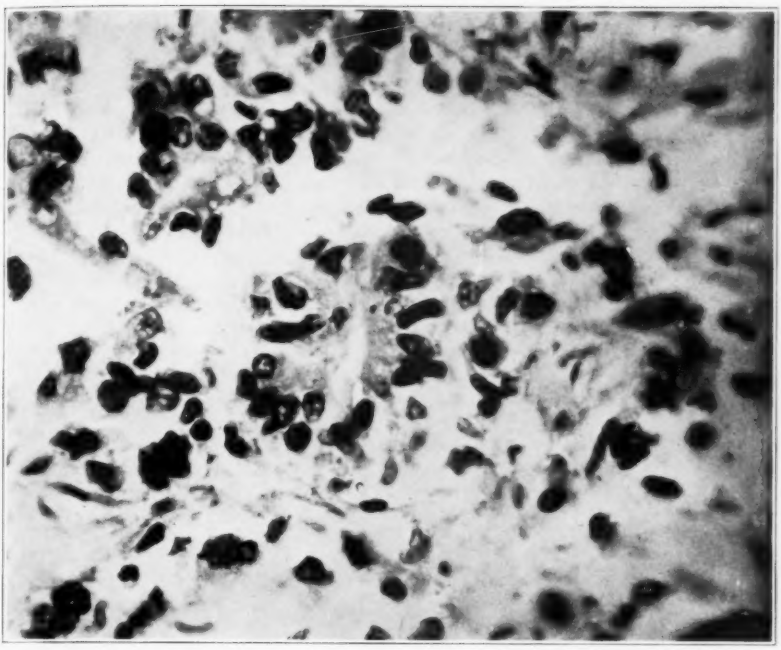

Fig. 1 (case 1).—High power magnification showing multinucleated cells and their variation in size and staining quality.

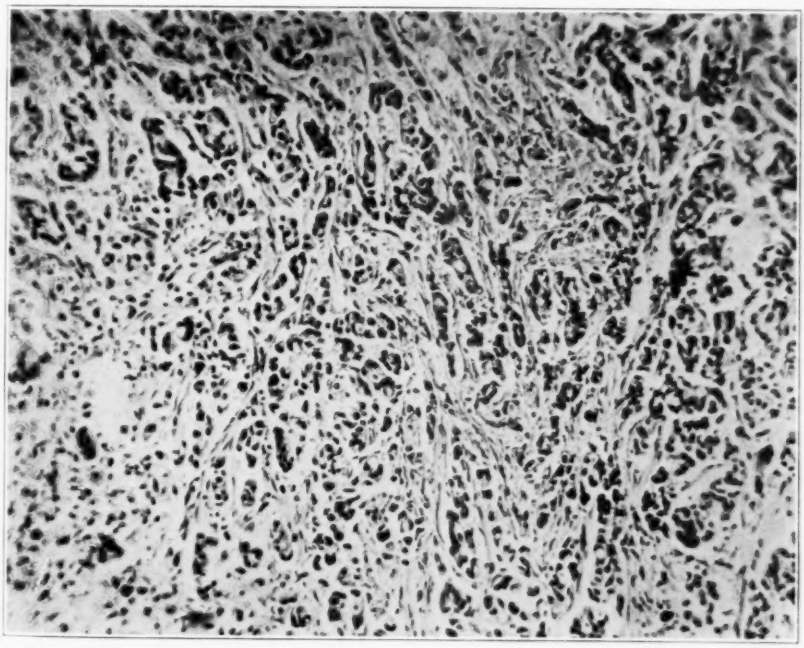

Fig. 2 (case 1).—Photomicrograph, showing infiltration of the muscular layer and the new formation of glandular structures.

mucosa, submucosa and muscularis and involved the head of the pancreas to some degree. On cut section, it was grayish yellow, but showed a few greenish, more or less circumscribed regions. The common duct opened into the midst of the tumor. The papilla of Vater was completely destroyed. The jejunum and remainder of the gastro-intestinal tract contained a large amount of partly liquid and partly clotted blood. The pancreas was bright yellow, soft and friable. On cut section, hardly any pancreatic tissue could be made out. The pancreatic duct was distended and filled with an almost clear liquid. The liver was enlarged and rather soft and green. There were a few small, circumscribed, yellow and umbilicated nodules throughout the surface. On cut section, they extended into the

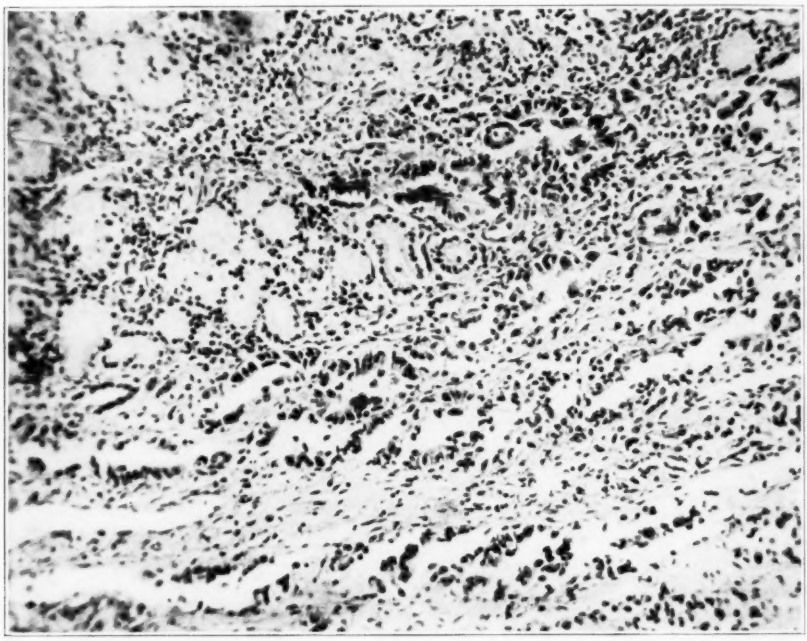

Fig. 3 (case 1).—Photomicrograph, showing infiltration in the muscular layer and the new formation of glandular structures, as in figure 2.

tissue of the liver. On cut section, the liver showed dilated central zones; the bile ducts were distended. The gallbladder was markedly distended, and contained a large amount of almost clear, slightly greenish-tinged bile. The hepatic and common ducts were dilated, measuring as much as 3 cm. in diameter.

Microscopic Observations: The mucosa and submucosa of the duodenum showed a new formation of glandular structures which were lined by one or two layers of rather high cylindric cells; these cells showed a marked variation in size, shape and staining quality. Mitotic figures were frequent. Some of the cells showed two or three nuclei. An infiltration in the muscular coats was seen in some fields. The parenchyma of the pancreas was almost completely replaced by

a new formation of connective tissue which was richly infiltrated with lymphocytes and endothelial cells. Large numbers of islands of Langerhans were present. The large ducts of the parenchyma were distended.

Diagnosis.—The following anatomic diagnosis was made: primary carcinoma of the duodenum (papilla of Vater), with extension to the head of the pancreas and metastases to the liver; hemorrhage of the stomach and intestines; marked dilatation of the gallbladder and of the bile and pancreatic ducts; atrophy of the pancreas; jaundice, secondary anemia, healed endocarditis of the mitral valve and pulmonary emphysema.

Fig. 4.—Gross specimen of the duodenum showing the tumor mass in the region of the papilla.

We report this case as one of primary carcinoma of the duodenum, although objections might be raised because of the destruction of the papilla. However, there was no malignant infiltration of the remaining portion of the duct. While it is true that this is possible even though the tumor is primarily of the papilla, the annular mass in the duodenum lends more favor to the view that this condition is a primary duodenal carcinoma. The discussion of the pathology will emphasize the difficulty of differentiating between the two conditions.

Case 2.—*History.*—J. J., a colored man, aged 36, married, was admitted to the Cook County Hospital on Aug. 9, 1929, complaining of pain in the stomach, jaundice, vomiting, clay-colored stools and a loss of 30 pounds (13.6 Kg.). Three weeks previously, a severe cutting pain localized in the epigastrium and associated with dizziness and faintness suddenly developed. The intensity of the pain subsided somewhat within a few hours, but remained to the time of examination. Shortly after the onset, the patient vomited, the character of the vomitus being unknown; vomiting had recurred after each meal. Since this acute onset, clay-colored stools, jaundice, itching of the skin, constipation, frequent gaseous eructations and occasionally fulness after eating had been noted. The appetite had become poor, and within a period of three months the patient had lost 30 pounds (13.6 Kg.).

Fig. 5 (case 2).—Gross specimen showing a tumor of the second part of the duodenum.

Examination.—The patient was well developed and well nourished, and did not appear acutely ill. The sclerae were icteric. There was slight tenderness and rigidity in the epigastrium, but no masses were palpable. The blood pressure was 210 systolic and 150 diastolic. The urine contained bile. The Wassermann test gave a negative reaction.

Course.—The patient complained of a gnawing sensation in the epigastrium which awakened him at night; it appeared soon after supper and was relieved by belching. A mass was felt in the region of the gallbladder which appeared to be large, rounded and immobile. Roentgenograms of the stomach and the duodenum were normal. Seven days after admission, the patient suddenly passed into coma, the only premonitory symptom being a headache.

Diagnosis.—A tentative diagnosis of stones in the common duct, hypertension and cerebral hemorrhage on the left side was made.

Necropsy.—Necropsy was performed by Dr. Jaffe.

Gross Observations: Gross examination revealed that the abdominal cavity contained about 100 cc. of deep yellow, clear fluid; the liver was 6 cm. below the xiphoid process and at the costal arch. The second portion of the duodenum was greatly narrowed by a firm, circular mass that measured 4.5 cm. in its longitudinal diameter and from 1 to 1.5 cm. in thickness. This mass extended downward to about 0.5 cm. above the ampulla of Vater. The lumen admitted the middle finger with difficulty. The mucosa was thrown up into firm, light yellowish-pink folds. The first portion of the duodenum was infiltrated by fine pinkish-gray granules. The upper end of the infiltrated area was formed by the pyloric ring. The lowermost part of the second portion showed a diffuse deep greenish-brown discoloration of the mucosa. The liver weighed 1,770 Gm. Its surface was smooth and yellowish brown with distinct dark purplish centers; its consistency was diminished. On the cut surface it was grayish brown, mottled with yellowish brown. There were distinct, fine, yellowish-gray, acinar markings; the intrahepatic bile ducts were markedly dilated and filled with thick green bile. The gallbladder was distended about 11 by 7 cm.; the mucosa was deep green and the bile a dark green. The extrahepatic bile ducts were greatly dilated; the common duct admitted one finger easily; the ampulla of Vater was edematous and measured 6 mm. in diameter and 8 mm. in height. The pancreas was firm; the main duct was diffusely dilated, reaching 12 mm. in circumference in the region of the head; the lining was smooth and light grayish white, with a few bright red patches the size of a pinhead.

Microscopic Observations: Microscopic examination showed that the tumor was very cellular, the cells being arranged in the form of cords and smaller and larger alveoli. Here and there distinct glandular structures and irregularly shaped tubuli lined by high epithelium were found. The connective tissue septums contained large lipoid-filled histiocytes. The type cell was cuboidal or polyhedral. It had a slightly oxyphilic cytoplasm and a large round or oval nucleus, the chromatin of which was arranged in fine granules. There was a small basophilic nucleolus. Mitotic figures were numerous. The liver showed marked dilatation of the intercellular bile capillaries in the central portions of the acini. Thick casts of bile filled the capillaries, and bile droplets were found in the liver cells and the enlarged Kupffer cells. In the periphery of the acini, the liver cells were free from bile pigment and appeared well preserved, with occasional small lipoid granules. Much fat was seen in the Kupffer cells. The periportal tissue was infiltrated by lymphocytes and eosinophilic leukocytes.

Diagnosis.—The following anatomic diagnosis was made: adenocarcinoma of the second portion of the duodenum with marked narrowing of the lumen; metastases to the peripancreatic, periaortic, mesenteric and left supraclavicular lymph nodes; edema of the papilla of Vater; marked dilatation of intrahepatic and extrahepatic bile ducts and of the pancreatic duct; recent hemorrhage in the pons, perforating into the fourth ventricle; recent encephalomalacia in the left globus pallidus; eccentric hypertrophy of the heart; moderate sclerosis of the coronary

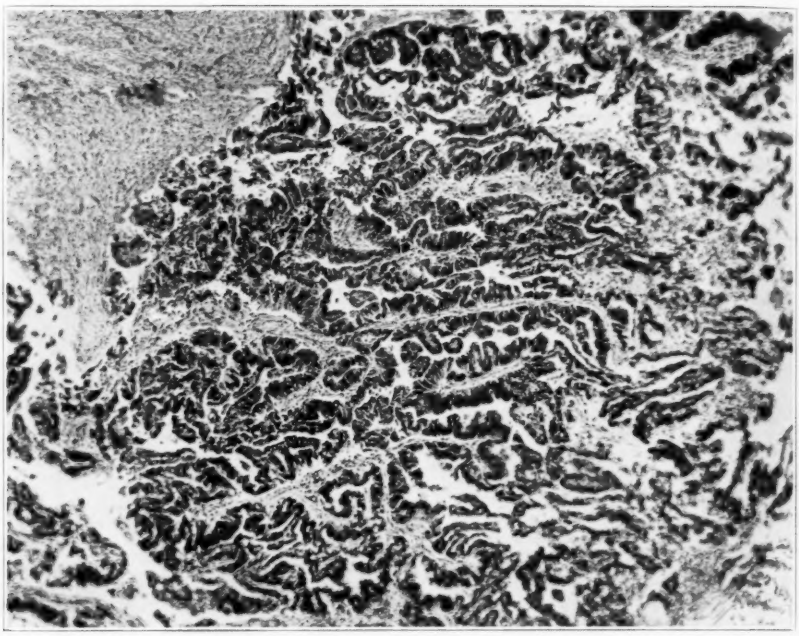

Fig. 6.—Photomicrograph showing glandular structures and irregular tubuli.

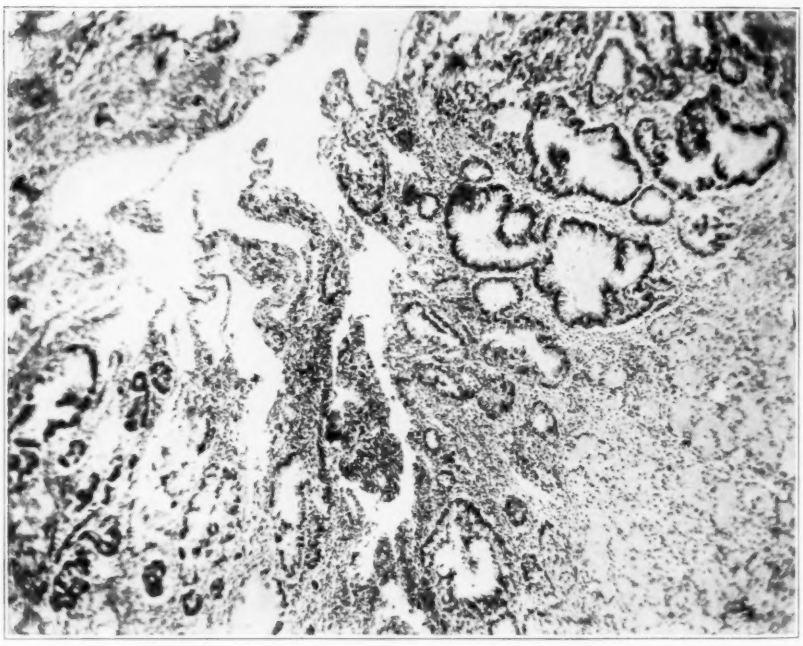

Fig. 7.—Photomicrograph showing the tumor invading the submucosa.

arteries and marked sclerosis of the cerebral arteries; marked icteric discoloration of the sclerae and internal organs; icteric nephrosis and arteriosclerosis of the kidneys; infectious softening of the spleen; hyperemia and edema of the lungs; slight ascites.

CASE 3.—*History.*—J. M., a white man, aged 55, married, was admitted to the Cook County Hospital on Feb. 10, 1929, complaining of epigastric pain, the loss of 50 pounds (22.7 Kg.) and clay-colored stools. The patient considered himself in excellent health until five months before admission, when transitory stabbing pain in the epigastrium had appeared after meals. The pain had recurred until three

Fig. 8.—High power magnification of figure 6. Note the presence of several layers of lining cells and mitotic figures.

months previous to admission, when it became more severe, continuous and burning. Food seemed to intensify the pain, and as a result he was afraid to eat. He was unable to sleep because of the intense pain. Gaseous eructations became frequent and bothersome. He was placed on a diet consisting of milk and crackers, and he was given "powders." Though the belching was relieved, the pain was unaffected. Six weeks previous to admission, nausea appeared and persisted to the time of admission. The appetite became poor. Three weeks previously, he had noted the appearance of clay-colored stools. Swelling of the ankles had been present for one week. He had lost 50 pounds (22.7 Kg.) in two months and had grown progressively weaker.

The past history revealed that the patient had had influenza in 1919. His wife had had three miscarriages. There were no children.

Examination.—The patient was well developed and emaciated, and he appeared quite ill. The skin had a light icteric hue. The sclerae were distinctly icteric. The abdomen was distended, with a tender mass palpable just to the right of the midline below the costal margin of the gallbladder. The edge of the liver was felt 2 cm. below the costal margin and was not tender. The other physical observations were normal. The blood pressure was 102 systolic and 68 diastolic.

The Wassermann reaction of the blood was negative. Examination of the blood showed: sugar, 136; urea nitrogen, 17.3; hemoglobin, 35 per cent; red cells, 2,400,000; white cells, 16,200; polymorphonuclears neutrophils, 94 per cent; small lymphocytes, 6 per cent and platelets, normal.

The urine was normal, except for a trace of bile; the stools were dark brown with occult blood. An Ewald test meal was given; after fifty-five minutes, the free hydrochloric acid was 34 and total acidity, 44.

A tentative diagnosis of carcinoma of the stomach with metastases to the liver, carcinoma of the bile ducts and carcinoma of the head of the pancreas was considered.

Course.—Roentgenograms of the stomach and duodenum gave normal results. The patient had a low grade fever continuously, the maximum temperature being 100.8 F. in the evening. The jaundice increased. On February 19, the icteric index was 37.5, and the van den Bergh reaction was negative. The patient grew progressively weaker. The anemia increased, and the leukocytes rose to 20,400. On the evening of February 21, he complained of sudden severe pain in the right hypochondrium radiating about the umbilicus; he died about nine hours later. A diagnosis of carcinoma of the pancreas was made.

Necropsy.—Necropsy was performed by Dr. Jaffe.

Gross Observations: Examination showed marked emaciation and anemia, and icterus of the skin, sclerae and mucous membranes. The abdomen contained 2,000 cc. of cloudy, light yellow fluid. The stomach was dilated and filled with bile-stained material. In the second portion of the duodenum, just below the papilla of Vater, there was a fungoid, soft, light gray mass, 5 cm. in length and 6.5 cm. in its transverse diameter, involving three fourths of the circumference of the duodenum and protruding about 10 mm. into the lumen. The common duct was greatly dilated, being 4 cm. in circumference. The hepatic duct was 6 cm. in circumference at the bifurcation; the cystic duct, 1.5 cm. in circumference, and the pancreatic duct, 7 mm. in circumference. The edge of the liver was 3 cm. below the xiphoid process and 2 cm. below the costal arch. The surface was studded with whitish hyaline plaques and yellowish-gray nodular elevations up to 4 mm. in diameter. The cut surface was deep brown; the intrahepatic bile ducts were dilated, being as much as 6 mm. in diameter. Smaller branches were transformed into anastomosing abscess-like cavities filled with thick yellowish-green pus.

Microscopic Observations: The tumor showed large, wide, irregular glands with papillary infoldings that were lined by a high and markedly anaplastic columnar epithelium. These glands extended throughout the duodenal wall, growing along the lymph vessels. There was an intensive inflammatory reaction in the form of leukocytic and plasmocellular infiltrations.

In the liver, the periportal tissue was much increased and contained dense accumulations of leukocytes and large lipophages and cells filled with golden brown pigment granules. Most of the cells of the liver appeared well preserved, except for areas of compression where the cellular accumulations bordered on the parenchyma.

Diagnosis.—The following anatomic diagnosis was made: medullary carcinoma of the second portion of the duodenum; marked dilatation of the extrahepatic and intrahepatic bile ducts, and intrahepatic purulent cholangeitis, diffuse serofibrinous peritonitis with chronic tumor of the spleen; brown atrophy and cloudy swelling of the liver and myocardium; serous atrophy of the epicardial fat tissue, bilateral hydrothorax and hydropericardium; fibrinous pleuritis of the right side and compression atelectasis of the right pulmonary lobe; confluent bronchopneumonia of the lower lobe of the left lung; cloudy swelling and cyst formation of the kidneys; decrease of lipoid content of the suprarenal cortex; icterus levis; inflammatory hyperplasia of the peripancreatic and peribiliary lymph nodes; aqueous and gaseous distention and edema of the intestines.

Case 4.—*History.*—F. O., a white man, aged 60, married, was admitted to the Cook County Hospital on June 9, 1927, complaining of indigestion, vomiting, loss of weight and weakness. He had enjoyed perfect health until about seven months previously, when he had vomited two or three hours after a meal. The vomitus was copious and green. The vomiting recurred every two or three days for a period of ten weeks, and appeared about two hours after meals. During this time, the patient lost weight steadily and became weaker. He had been under medical treatment for an ulcer during this time. A gastro-enterostomy was performed later at one of the local hospitals, from which he was making an uneventful recovery, until, "after the wrong tray," pain suddenly developed in the umbilical region and lasted for about two hours. He left the hospital, and a short time later entered Cook County Hospital. At this time, he had abdominal cramps that usually appeared after meals and were relieved by enemas. Throughout his illness, his appetite remained good, yet he lost 50 pounds (22.7 Kg.). Dyspnea had been present since the onset.

Examination.—The patient was fairly well developed, but markedly emaciated, and appeared to be quite sick. Tenderness and the suggestion of a mass in the epigastrium were noted. The stomach was dilated. There were visible peristaltic waves, with audible gurgling sounds. The ankles pitted on pressure. The other observations were normal. The urine was normal. Examination of the blood gave normal results. The Wassermann reaction was negative.

The following diagnosis was made: pyloric obstruction due to a malignant condition or adhesions; ulcer at the site of enterostomy, and a malignant condition of the bowel.

Course.—The basal metabolic rate was plus 10. Roentgenograms showed: "30 per cent gastric retention; the pyloric region appeared defective on the screen; the stomach was in a position too high to palpate satisfactorily. The bulb was not well visualized. Marked stasis, surging and dilatation of a peculiarly looped or circled duodenal curve including the first, second and part of the third portions was noted. Suggestion of delay or impediment in the third portion of the duodenum was presumed." One hour after an Ewald meal was given, 230 cc. of the stomach contents showed: free hydrochloric acid, 5; total acidity, 18. Seven hours after a motor meal was given, 170 cc. was obtained by tube; few remains of the meal were present. The patient became progressively weaker and died on June 18.

Necropsy.—Necropsy was performed by Dr. Jaffe.

Gross Observations: The stomach was moderately distended and adherent to the surrounding structures by adhesions. A gastrojejunostomy had been performed. The first portion of the duodenum was closed surgically. At about 10 cm. from the stump, there was an irregularly round opening, surrounded by a hemorrhagic, soft, fungating, slightly pedunculated area 2 by 5 cm.

Microscopic Observations: Microscopically, the tumor was a papillary adenocarcinoma.

Diagnosis.—The following anatomic diagnosis was reported by Dr. Jaffe: huge, ulcerating, perforated carcinoma of the third portion of the duodenum; secondary generalized fibrinopurulent peritonitis with bilateral subphrenic abscesses; serofibrinous pleurisy of the left side; band of adhesions between the omentum and the laparotomy scar with partial strangulation of several small intestinal loops; ancient gastric resection with a functioning gastrojejunostomy, subacute splenic tumor, passive hyperemia of the lungs; atherosclerosis of the aorta and coronaries; chronic periappendicitis; moderate-sized adenoma of the prostate; diverticulum of the jejunum; multiple rectal polypi; icterus levis; anemia.

INCIDENCE

In 1901, Rolleston [6] stated that primary carcinoma of the duodenum is "decidedly rare." As recently as 1926, Cabot [7] also remarked that it is "very rare." Even considerable variation in this respect, as shown particularly in table 3, obviously is not beyond expectation, yet from a compilation of statistics appearing in the literature, some degree of unanimity is apparent. Primary duodenal carcinoma is found in from 0.01 to 0.1 per cent of all postmortem examinations with the common figures being from 0.01 to 0.03 per cent (table 1). Our cases were found among a total (Cook County and Michael Reese Hospitals) of 10,876 necropsies, an incidence of 0.037 per cent.

If one studies the relation of this lesion to carcinomas in general, one finds that from 0.04 to 1.1 per cent are in the duodenum, more commonly from 0.2 to 0.4 per cent (table 2).

Of the relation of duodenal carcinoma to intestinal carcinomas, much may be said. Whereas as high an incidence as 26 per cent has been reported in the duodenums (Kohler [8]), its frequency is more commonly quoted as being from 1.5 to 4 per cent, with a low maximum, 5.7 per cent (Geiser [9]) (table 3). It is known that carcinoma occurs far less commonly in the small intestine than in the large. According to Brill's [10] collected statistics (1904), only 2.5 per cent of intestinal carcinomas are in the small bowel, the duodenum and the ileum being involved with equal frequency. Rolleston,[6] Bland-Sutton,[11] Jefferson [12]

6. Rolleston, H. D.: Carcinomatous Stricture of the Duodenum, Lancet **1**: 1121 (April 20) 1901.

7. Cabot, R.: Case Records, Boston M. & S. J. **194**:267 (Feb. 11) 1926.

8. Kohler, quoted by Forgue, E., and Chauvin, E.: Rev. de chir. **50**:470 (Dec.) 1915.

9. Geiser, J. F.: Ueber Duodenalkrebs, Deutsche Ztschr. f. Chir. **86**:41, 1906.

10. Brill, N. E.: Primary Carcinoma of the Duodenum, Am. J. M. Sc. **128**: 824, 1904.

11. Bland-Sutton, J.: On Cancer of the Duodenum and Small Intestine, Tr. M. Soc. London **38**:1 (Oct. 12) 1914.

12. Jefferson, G.: Carcinoma of the Suprapapillary Duodenum Casually Associated with Preexisting Simple Ulcer: Report of a Case, and an Appendix of Thirty Collected Cases, Brit. J. Surg. **4**:209 (Oct.) 1916.

TABLE 1.—*Percentage of Cases of Primary Duodenal Carcinoma Found at Necropsy*

	Necropsies	Duodenal Carcinoma	Percentage
Perry and Shaw: Guy's Hosp. Rep. **50**: 171, 1893	17,652	4	0.020
Fenwick and Fenwick: Cancer and Other Tumors of the Stomach, London, 1902	19,518	18	0.090
Maydl: Ueber den Darmkrebs, Vienna, 1883	20,480	5	0.010
Nothnagel: Spez. Path. u. Therap. **17**: 220, 1898	21,358	5	0.020
Zemann, quoted by Brill: Am. J. M. Sc. **128**: 824, 1904	21,624	3	0.013
Muller, M.: Inaugural Dissertation, Berne, 1892	5,621	6	0.100
Deaver and Ravdin: Am. J. M. Sc. **159**: 469, 1920	151,201	70	0.033
Schlesinger: Wien. klin. Wchnschr. **11**: 245, 1898	42,000	7	0.017
Rulp, quoted by Forgue and Chauvin: Rev. de chir. **50**: 470, 1915	4,258	1	0.023
Tiemann: Beitrage zur Pathologie und Statistik des Krobses, Kiel, 1900	3,350	2	0.060
Geiser: Deutsche Ztschr. f. Chir. **86**: 41, 1906	11,314	7	0.062
Meyer and Rosenberg	16,876	4	0.037

TABLE 2.—*Percentage of Duodenal Carcinoma Among Cases of Carcinoma in General*

	Carcinoma in General	Duodenal Carcinoma	Percentage
Muller, M.: Inaugural Dissertation, Berne, 1892	521	6	1.10
Lubarsch: Arch. f. path. Anat. **111**: 280, 1888	569	2	0.35
Brill: Am. J. M. Sc. **128**: 824, 1904	4,675	15	0.30
Schlesinger: Wien. klin. Wchnschr. **11**: 245, 1898	3,583	7	0.20
Jefferson: Brit. J. Surg. **4**: 209, 1916	.....	..	0.04
Rulp, quoted by Forgue and Chauvin: Rev. de chir. **50**: 470, 1915	372	1	0.27
Tiemann: Beitrage zur Pathologie und Statistik des krobses, Kiel, 1900	478	2	0.40
Geiser: Deutsche Ztschr. f. Chir. **86**: 41, 1904	909	7	0.77

TABLE 3.—*Percentage of Duodenal Carcinoma Among Cases of Carcinoma of the Intestines*

Authors	Carcinoma of Intestine	Duodenal Carcinoma	Percentage
Forgue and Chauvin: Rev. de chir. **50**: 470, 1915	888	42	4.5
Leichtenstern, quoted by Brill: Am. J. M. Sc. **128**: 824, 1904	770	30	4.0
Geiser: Deutsche Ztschr. f. Chir. **86**: 41, 1906	123	7	5.7
Bryant, quoted by Brill: Am. J. M. Sc. **128**: 824, 1904	110	6	5.5
Muller, F., quoted by Kaufmann: Lehrbuch der speziellen pathologischen Anatomie, 1922	123	5	4.0
Zemann, quoted by Brill: Am. J. M. Sc. **128**: 824, 1904	165	5	3.0
Rulp, quoted by Forgue and Chauvin: Rev. de chir. **50**: 470, 1915	33	1	2.9
Maydl: Ueber den Darmkrebs, Vienna, 1883	100	2	2.0
Ewald, quoted by Syme: Lancet **1**: 148, 1904	1,148	19	1.7
Nothnagel: Spez. Path. u. Therap. **17**: 220, 1898	243	5	2.0
Schlesinger: Wien. klin. Wchnschr. **11**: 245, 1898	443	7	1.6
Jefferson: Brit. J. Surg. **4**: 209, 1916	4,177	54	1.3
Eichhorst: Handb. d. spez. Path. u. Therap. **2**: 234, 1890	34	9	26.0
Judd: Journal-Lancet **39**: 159, 1919	1,846	5	0.27
Haussmann: Etiologie et pathogenie du cancer de l'intestin, Thèse de Paris, 1882	285	0	0
Meyer and Rosenberg (Cook County Hospital)	569	3	0.53

and Deaver and Raydin,[13] however, stated that the duodenum is the most common site for carcinoma of the small intestine. Brill [10] was able to find no instance of primary jejunal carcinoma, but since his paper appeared its incidence has greatly increased. Lahey [14] in 1915, Jefferson [12] in 1916 and Judd [15] in 1919 reported on twenty-four cases of carcinoma of the small intestine; they found eleven cases in the jejunum, five in the duodenum, six in the ileum and two with multiple involvement. In 1925, Eusterman, Berkman and Swan [16] found fifteen of thirty-nine carcinomas of the small intestine localized in the duodenum.

We endeavored to study this relationship from the clinical records available at the Cook County Hospital. As diagnostic criteria we accepted the following: (1) physical observations; only rectal or proctoscopic examinations were considered sufficiently accurate; (2) roentgen examination showing an irregular filling defect, in conjunction with occult blood in the stool; (3) the surgeon's diagnosis based on the appearance at the time of operation; (4) biopsy report; (5) postmortem examination. Table 4 shows our observations.

TABLE 4.—*Incidence of Carcinoma in Various Parts of the Intestines*

Duodenum	3	Transverse colon	14
Duodenojejunal junction	1	Splenic flexure	10
Ampulla of Vater	3	Descending colon	4
Jejunum	3	Sigmoid colon	66
Obendorf tumor*	12	Rectum	365
Ileum	3	Ileum, cecum and ascending colon	1
Appendix	1	Ascending and transverse	1
Cecum	30	Cecum, ascending and hepatic flexure	1
Ileocecal	2	Transverse and splenic flexure	1
Ascending colon	8	Rectosigmoid junction	12
Hepatic flexure	5	Colon	4
Total			569

* Personal communication with Dr. Richard Lifvendahl, taken from his unpublished reports.

Of 569 clinical cases of intestinal carcinoma, 3 were located in the duodenum, primarily, and 1 was at the duodenojejunal junction. If we disregard the latter, the incidence in our series is 0.53 per cent.

13. Deaver, J. B., and Raydin, I. S.: Carcinoma of the Duodenum, Am. J. M. Sc. **159**:469 (April) 1920.

14. Lahey, F. H.: Carcinoma of the Small Intestine, Am. J. Surg. **62**:428 (Oct.) 1915.

15. Judd, E. S.: Carcinoma of the Small Intestine, Journal-Lancet **39**:159 (April 1) 1919.

16. Eusterman, G. B.; Berkman, D. M., and Swan, T. S.: Primary Carcinoma of the Duodenum: Report of Fifteen Verified Cases, Am. J. Surg. **82**:153 (July) 1925.

In addition to the cases previously cited and those in the tables, Rolleston,[6] Deaver and Raydin,[13] Cabot,[7] Bibby and Stewart,[17] Head,[18] Pommay and Seille,[19] Jefferson,[12] Letulle,[20] Geiser,[9] Skillern,[21] Pauchet and Luquet[22] and Syme[23] contributed reports of single instances. Dewis and Morse[24] recently reported twelve cases.

ETIOLOGY

In the majority of cases, duodenal carcinoma makes its appearence without any recognizable cause. Males are more frequently attacked than females, the predominance varying with the author, the ratio being 3:1 according to Rolleston,[6] or 8:5 according to Pic.[25] All of our patients were males.

Duodenal carcinoma usually occurs in late middle and advanced life, the average age being 52 years. The average age of our patients was 49, corresponding with that of Forgue and Chauvin.[26] It has been encountered as early as 16 years (Ewald[27]) and as late as 80 (Perry and Shaw[28]).

No racial predilection is notable.

In an attempt to elucidate the pathogenesis of this condition, many theories have been propounded. Geiser[9] suggested two theories: 1. The condition is caused by irritation; a fold of mucosa becomes

17. Bibby, J. P., and Stewart, M. J.: Primary Carcinoma of the First Part of the Duodenum with Secondary Involvement of the Common Bile Duct, Lancet **1**:525 (Feb. 21) 1914.

18. Head, G. D.: Primary Carcinoma of the Third Portion of the Duodenum, Am. J. M. Sc. **157**:182 (Feb.) 1919.

19. Pommay, S., and Seille: Un cas de cancer de la quatrième portion du duodénum, Ann. d'anat. path. **2**:141 (March) 1925.

20. Letulle, M.: Cancer colloïde du duodénum développé sur un ulcère simple, Bull. Soc. anat. de Paris **72**:721 (Oct.) 1897.

21. Skillern, P. G.: Cancer of the Duodenum, Pancreas and Pylorus, Internat. Clin. **3**:158, 1914.

22. Pauchet, V., and Luquet: Cancer de la quatrième portion du duodénum, Bull. Acad. de méd., Paris **97**:276 (March 1) 1927.

23. Syme, G. A.: Carcinoma of the Duodenum: Resection; Recovery, Lancet **1**:148 (Jan. 16) 1904.

24. Dewis, J. W., and Morse, G. W.: Primary Carcinoma of the Duodenum: Report of Twelve Proved Cases; Summary of Literature, New England J. Med. **198**:383 (April 12) 1928.

25. Pic, A.: Contribution à l'étude du cancer primitif du duodénum, Rev. de méd. **14**:1081 (Dec.) 1894; **15**:56 (Jan.) 1895.

26. Forgue, E., and Chauvin, E.: Le cancer primitif et intrinsèque du duodénum, Rev. de chir. **50**:470 (Dec.) 1915.

27. Ewald, C. A.: Ein Fall von Atrophie der Magenschleimhaut mit Verlust der Salzauresecretion: Ulcus carcinomatosum duodenale, Berl. klin. Wchnschr. **23**:527 (Aug. 9) 1886.

28. Perry, E. C., and Shaw, L. E.: On Diseases of the Duodenum, Guy's Hosp. Rep. **50**:171, 1893.

chronically irritated by the duodenal contents. 2. In the area contiguous to the papilla of Vater, there is a conflict of two types of epithelial cells, with a resultant proclivity to carcinomatous degeneration, which explains the greater frequency of carcinoma at this part of the duodenum. Several predisposing factors based on the anatomic relations of the duodenum were discussed by Forgue and Chauvin.[26] The projection of the papilla into the lumen with irritation by food received consideration. The fixation of the duodenum by the parietal peritoneum, the four flexures and the difficulty in adapting itself to the contents were conceived as factors. Likewise, the duodenum was said to be the most dilated portion of the small intestine and hence to favor stasis and consequent irritation.

Chronic duodenal ulcer has been thought by some writers and investigators to predispose to the development of carcinoma, and while this relationship must be considered, *sub judice*, the consensus is negatory. Perry and Shaw [28] reported five cases (including one observed by Sidney Coupland) purported to have developed on the basis of an ulcer. Letulle [29] and Geiser [9] each reported a case. Ewald,[27] Schrötter,[29] Mackenzie [30] and Eichhorst [31] reported single instances (collected with Letulle's by Nattan-Larrier [32]). Jefferson [12] collected nineteen additional cases appearing in the literature and added one of his own. After critically reviewing the clinical and pathologic accounts, we must conclude, as Jefferson did, that "some are very doubtful." In 1900, Menetrier [33] investigated the relationship and concluded that a hyperplastic cellular reaction bordering on adenomas was produced near the ulcer and slowly developed into carcinoma. One would expect, then, to find carcinoma more frequently in the first portion of the duodenum, the common site of ulcer, whereas actually, the second portion is more commonly involved. Because of the rarity of ulcer-carcinoma and the uncertainty that surrounds any attempt to correlate the two, it is our belief that they may be coincidental.

By virtue of their irritation to the duodenum, gallstones have been mentioned as important in the explanation of the more frequent involvement of the second portion of the duodenum. In this respect, an interesting paradoxical observation was noted in Geiser's [9] study. Although cholelithiasis occurs more frequently in women and ulcer

29. Schrötter, L.: Aerztl. Ber. d. k.k. allg. Krankenh. zu. Wien, 1886, p. 27.

30. Mackenzie, H. W. G.: Duodenal Ulcer; Obstruction of Common Bile-Duct; Jaundice; Malignant Disease of Liver; Intestinal and Cerebral Hemorrhage, St. Thomas's Hosp. Rep. 1890-1891 **20**:341, 1892.

31. Eichhorst, H. L.: Handb. d. spez. Path. u. Therap. **2**:234, 1890.

32. Nattan-Larrier: Les cancers du duodénum, Gaz. d. hóp. **72**:1291 (Dec. 2) 1899; **72**:1311 (Dec. 7) 1899.

33. Menetrier, quoted by Forgue and Chauvin (footnote 26).

more often in men, carcinoma of the second portion of the duodenum occurred more frequently in men and that of the first portion more frequently in women.

Syphilis has been considered as a factor, but although occurring in the case of Dewis and Morse [24] and Curtis and Surmont [34] and in case 1 of our group, it is probably of no significance.

PATHOLOGY

Carcinomas of the duodenum are most often primary in origin. They are thought to arise from the mucosa, Brunner's glands (Orth), aberrant pancreatic tissue (Cohnheim) or aberrant stomach tissue (McGuire and Cornish [35]). In commenting on their origin, Bland-Sutton remarked that any theories implicating aberrant pancreatic tissue or Brunner's glands "belong to the domain of fiction."

Usually they are cylindric cell adenocarcinomas that have a tendency to encircle the duodenum, producing stenosis with proximal dilatation, muscular hypertrophy and chronic catarrhal inflammation. Some of them are spheroidal cell adenocarcinomas, taking the form of soft excrescences or of deep ulcers with elongated edges and fungated bases (Head [18]), these being difficult to distinguish from carcinoma arising in the ampulla, pancreatic duct or pancreas. They may be scirrhous, medullary or colloid (Brill [10]). They ulcerate frequently and occasionally perforate, producing peritonitis (case 4). Metastases appear late and are found in the liver, regional lymph nodes, pancreas and lungs and less commonly in the peritoneum, gallbladder, supraclavicular glands (case 2) and bones. Eichhorst [31] reported metastases to the bone marrow of the sternum. Geiser [9] called attention to their tendency to produce metastases in the liver and regional lymph nodes with compression of the common bile duct, thereby simulating carcinoma of the pancreas.

Pic [25] divided them into three types, namely: (1) parapyloric (formesus-vaterienne), (2) periampullary and (3) prejejunal (forme sous-vaterienne). The most common type is the periampullary; the most infrequent, the prejejunal.

The parapyloric type usually encircles the duodenum, producing stenosis with proximal dilatation, insufficiency of the pyloric ring and gastric dilatation. Its relation to peptic ulcer has already been discussed. Morrison and Feldman [36] reported an interesting case of primary para-

34. Curtis, F., and Surmont, H.: Cancer duo pylore d'origine duodénale chez un syphilitique, Arch. d. mal. de l'app. digestif **13**:24 (Jan.) 1923.

35. McGuire, E. R., and Cornish, P. G.: Carcinoma of the Duodenum, Am. J. Surg. **72**:600 (Nov.) 1930.

36. Morrison, T. H., and Feldman, M.: Autopsy Report of a Case of Primary Carcinoma in a Duodenal Diverticulum, Am. J. Clin. Med. **5**:326 (Oct.) 1926.

pyloric carcinoma that arose in a diverticulum and metastasized to the liver. They stated that this is the only case in the litertaure. No additional accounts have appeared since theirs.

The periampullary type usually arises in or about the papilla as an infiltration about the size of a walnut or cherry; it tends to encircle and extend along the duodenum (Nothnagel[37]). It is difficult to differentiate this type from carcinoma of the ampulla (case 1). The latter, however, is sharply circumscribed about the papilla (Nothnagel[37]). Attention is called to the difficulty of recognition of the true primary origin of carcinoma of the second portion of the duodenum by histologic examination. The papilla that may be the site of a primary tumor may reveal histologic evidence of carcinoma along the duct, but this may fail to aid in differentiation. Geiser made the point that a lesion originating from the papilla may show carcinomatous changes along the lumen of the duct, but even this is not positive for the duct may be secondarily involved from the primary duodenal lesion. Obstruction to the flow of biliary and pancreatic juices is produced, leading to dilatation of the bile ducts and capillaries, distention of the gallbladder, increase in the size of the liver with subsequent increase in connective tissue and cirrhosis, dilatation of the pancreatic ducts and pancreatic atrophy (case 1). With ulceration of the tumor, the resultant signs and symptoms of biliary obstruction and pancreatic disease disappear (case 1). Occasionally, death may follow erosion of the blood vessel (case 1). In other cases, infection develops in the biliary tract, which leads to a suppurative cholangeitis with intrahepatic abscesses (case 3).

The prejejunal form is most often broad, flat and ulcerated. Stenosis develops, with dilatation of the proximal segments, namely, the duodenum, the pyloric ring and the stomach.

SYMPTOMS

The onset of the condition is variable. It may be sudden or insidious. Most commonly, it manifests itself by the appearance of nausea, progressive loss of appetite and weight, gaseous eructations, heartburn, jaundice or epigastric discomfort (fulness or dull pain), which usually occurs two or three hours after meals and is relieved by the use of soda or by vomiting. Sometimes the patient's attention is first arrested by the perception of a tumor mass in the epigastrium, the right hypochondrium or the umbilical region. At other times hematemesis is the first symptom. Rarely, progressive asthenia, emaciation and swelling of the abdomen from ascites are first noted.

37. Nothnagel, quoted by Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1919, p. 641.

With the progress of the disease, pain usually becomes more prominent. It may be burning or intermittent and cramplike; it usually appears in the epigastrium or the right hypochondrium two or three hours after meals and is relieved by vomiting. Yet there may be no relation to meals. This pain has been explained in various ways, namely, (1) contraction of the stomach or intestine against an obstruction; (2) compression of the celiac axis by the tumor; (3) distention of the liver or gallbladder from biliary stasis.

Vomiting appears with the development of the obstruction. At first it is noted from the one-half to one hour after eating. Later, it occurs immediately after eating. Still later, it becomes less frequent, that is, once daily, but is abundant. Ultimately, owing to the ulceration of the tumor and relief from the obstruction, it may cease. Repeated vomiting results in an increased thirst, oliguresis and dehydration.

Jaundice, a common symptom, usually increases in intensity. It is due to an obstruction at the ampulla of Vater by the tumor or by edema of the papilla, to hepatic metastases or to compression of the common bile duct by the lymph nodes. However, it may become intermittent, consequent to ulceration of the tumor.

Constipation is common, owing either to progressive intestinal obstruction or to recurrent vomiting. At times it may alternate with diarrhea. The stools may be clay-colored, black or normal.

Fever is usually absent until late, when it is often due to ulceration of the tumor.

In some respects the clinical picture varies with the part of the duodenum affected. The parapyloric type usually does not produce icterus. It simulates pyloric obstruction so closely that it is almost impossible to differentiate the two conditions. The prejejunal type differs from the parapyloric by the presence of bile and pancreatic ferments in the vomitus, the differentiation having been first made by Chomel.[4] Pommay and Seille[19] pointed out the longer latent period during which general symptoms of malignancy dominate. The periampullary type simulates the parapyloric when the tumor is located above the papilla, and the prejejunal when the tumor is below the papilla. When the tumor is located at the papilla, a progressive, painless, obstructive and sometimes intermittent jaundice results, with few if any gastro-intestinal symptoms. Biliary and pancreatic obstruction, ascending cholangeitis and hepatic abscesses are more likely to develop here. In the event of pancreatic obstruction, the stools become large, pale, fatty and offensive.

PHYSICAL EXAMINATION

Our attention was directed to the pallor and emaciation and, in instances of recurrent vomiting, to the dehydration. Icterus is com-

monly present. The abdomen is flat and soft; epigastric distention is rarely detected. Peristaltic waves may be visible across the upper part of the abdomen, and sometimes the outlines of a dilated stomach and duodenum may be seen or percussed. Frequently, a tumor mass may be felt, and while it is usually located in the epigastrium to the right of the midline, it may be found in the right hypochondrium or in the region of the umbilicus. The tumor mass is hard, irregular and, when parapyloric, mobile. The periampullary and prejejunal forms show little if any mobility. The gallbladder is usually distended, tense and easily delimited. The liver is commonly enlarged, firm, smooth and not tender. Enlarged supraclavicular glands are occasionally found. In the advanced stages, ascites, metastatic peritoneal implantations and a nodular liver may be revealed. Gastric succussion is sometimes elicited.

LABORATORY OBSERVATIONS

In a large proportion of cases, the contents of the stomach show a diminution or absence of free hydrochloric acid. Sometimes the gastric acidity is normal. It is not common to find blood, except in advanced cases with malignant ulceration associated with insufficiency of the pylorus. Of the greatest diagnostic import is the presence of bile and trypsin in all cases of obstruction below the papilla. Gastric retention is encountered in the later stages of all duodenal carcinomas.

The stools vary in character, depending on the presence or absence of ampullary obstruction. In the former, they are acholic, and with the progress of pancreatic degeneration they become offensive and bulky, with undigested meat fibers and starch and an excess of neutral fats. Occult blood is found in all of them.

The urine contains an increased amount of indican and creatinine. Bile is detected in cases of biliary obstruction; with pancreatic changes, dextrose may be found.

The blood shows varying degrees of anemia, with a greater decrease in the hemoglobin content as compared with the erythrocytic count; whereas leukocytosis is common as part of the picture of anemia, a further increase may be noted, the result of malignant ulceration. The differential formula shows an increase in polymorphonuclear neutrophils. Hyperglycemia may be present, and it is usually associated with advanced pancreatic changes. In instances of repeated vomiting, elevation in the carbon dioxide-combining power and lowering of the chlorides may be demonstrated (alkalosis). The blood urea is increased.

ROENTGEN EXAMINATION

The site of the malignant process is revealed, and if the process has advanced to the point of producing stenosis, proximal dilatation of the duodenum and stomach and gastric hypomotility may be observed.

COMPLICATIONS

Secondary growths are common in the late stages, especially in the liver, regional lymph nodes and adjacent structures. Ascites may develop from peritoneal carcinosis. Forgue and Chauvin [26] referred to the occurrence of a duodenocolic fistula that resulted from adhesions to the colon and produced diarrhea.

Geiser [9] observed a case of compression of the ureter with hydronephrosis. Often a suppurative cholangeitis with intrahepatic abscesses and empyema of the gallbladder is seen in the terminal stages. The primary growth may ulcerate, perforate and produce a peritonitis (case 4) with subphrenic, retroperitoneal or peri-intestinal abscesses. Phlebitis of the portal vein, the inferior vena cava, the iliac and the hypogastric and femoral veins, with corresponding ascites or edema of the lower extremities, or both, has been reported. A sudden severe hemorrhage with hematemesis and melena from erosion of a large vessel may terminate the picture (case 1).

COURSE

The course is usually chronic, lasting from three to eighteen months, the average being seven months after the first appearance of symptoms. The anemia, asthenia, emaciation and cachexia progressively increase; commonly, oft-repeated vomiting eventuates. Death has been known to occur in a few days, rarely later than after two months, in the cases in which there is severe vomiting and in which surgical intervention is not attempted. Death may be the result of great emaciation and gradual exhaustion, intercurrent infection, especially bronchopneumonia, peritoneal complications or hemorrhage.

DIAGNOSIS

The diagnosis is most difficult. Geiser [9] said that the diagnosis of the parapyloric type has not been made by physical examination. Owing to the rarity of carcinoma of the duodenum, it is seldom suspected. A person who is well past middle age and who gives a history of epigastric distress of relatively short duration is more apt to be suspected of having a carcinoma of the stomach than a carcinoma of the duodenum. Forgue and Chauvin [26] noted that in only two of forty-five cases was the true diagnosis suspected. The absence of a distinctive symptom-complex is probably equally important as a cause for failure in diagnosis. Such symptoms as pain in the epigastrium after meals, vomiting and other evidence of retention speak for stenosis—pyloric or duodenal. The presence of greater mobility of the duodenum than of the pylorus is of little value in differentiating parapyloric duodenal carcinoma from

carcinoma of the pylorus. The claim of some that free hydrochloric acid is present in the gastric contents in cases of parapyloric carcinoma (duodenal) as contrasted with achlorhydria in carcinoma of the pylorus (gastric) is disputed by Geiser, who asserted that parapyloric carcinoma (duodenal) becomes noticeable only when it has resulted in gastric dilatation, and by that time the gastric acidity is nil, as in carcinoma of the pylorus.

The periampullar type of duodenal carcinoma, which is the most common form, causes even greater difficulties in diagnosis. The gradual development of a symptom-complex, such as progressive jaundice, enlargement of the gallbladder, vomiting, acholic stools and the absence of tryptic digestion, makes the differentiation from carcinoma of the head of the pancreas impossible. In such cases, roentgen evidence is also of little aid; gallstones are probably easily differentiated, but such conditions as carcinoma of the papilla, carcinoma of the gallbladder and chronic interstitial pancreatitis can be diagnosed with certainty only at operation and on histologic examination. Of some clinical value may be the fact that carcinoma of the biliary tract, as well as carcinoma of the papilla, tends to produce early metastases, whereas the periampullar type of duodenal carcinoma produces metastases late. Carcinoma of the papilla is more likely to be associated with an intermittent jaundice, while in carcinoma of the duodenum the jaundice is of the obstructive type and diminishes only with extensive ulceration of the tumor.

The prejejunal variety of duodenal carcinoma is marked by gastric dilatation, a variability in gastric acidity, associated presence of bile and pancreatic juices and trypsin in the gastric contents. Attacks of acute abdominal pain and severe vomiting are not uncommon. The foregoing symptomatology calls for the differentiation from carcinoma of the jejunum and carcinoma of the pylorus (stomach). The roentgen rays should be of value in differentiating definitely from the latter. Further, free hydrochloric acid is more likely to be present in the prejejunal type of duodenal carcinoma than in carcinoma of the pylorus. In carcinoma of the pylorus there is usually no bile, trypsin or pancreatic juice. Occasionally, in carcinoma of the pylorus with insufficiency of the pyloric ring, there is a regurgitation of bile and pancreatic juice (Geiser[9]), thus making the differentiation from prejejunal carcinoma most difficult.

The absence of marked abdominal distention, associated with a symptom-complex of intestinal obstruction, points with greater probability to a lesion being located in the small than in the large bowel. Likewise, the vomiting of feculent material is ascribed by Geiser[9] as being more likely in the jejunum than in the duodenum.

It is important to bear in mind the possible confusion of carcinoma of the duodenum with an ulcer of the duodenum in very old persons. This is especially true in duodenal ulcer with obstruction. Like carcinoma of the stomach, carcinoma of the duodenum has a history of relatively short duration. It is not an uncommon experience to observe acute ulcers of the duodenum in persons past 50 or 60 years of age. Some of these, it is true, are not acute, but have a chronic history. In an analysis of thirty-eight cases of duodenal ulcer [38] in persons past 50, the following data were noted relative to duration. In eleven cases, the duration was from ten to seventeen years; in six cases, from two to five years; in seven cases, from one month to one year; in nine cases, from two to nine weeks; in three cases, no definite history, and in one, twenty-six years. The occurrence in sixteen instances of duodenal ulcer in persons past 50 with a history of duration varying from two weeks to one year is significant enough to direct attention to the possibility of a malignant process. The general tendency of the clinician is to regard the person past middle age with a history indicating ulcer as having either a gastric ulcer or a gastric carcinoma. While these are unquestionably the most likely possibilities, some of the cases may prove to be duodenal carcinoma (case 4).

While recognizing the difficulty of diagnosis of duodenal carcinoma both clinically and histologically, we raise the question whether careful study may not reveal an increasing number of duodenal carcinomas. Analogous to this is the now well recognized fact that the majority of the so-called pyloric stenoses are on the duodenal side. It is also interesting to note the careful studies of Nagel,[39] who reported slight involvement of the duodenum in five of fourteen cases of cancer of the pylorus.

Lest we be misunderstood, we wish to emphasize the difficulties of definite diagnosis of primary carcinoma of the duodenum and the necessity of careful, critical, histologic study of all tissues. Thus in a review of the cases at Michael Reese Hospital, we encountered one case which on histologic examination showed malignant infiltration of a duodenal scar. The gross impression of the pathologist was that of an old scar from an ulcer. Histologic examination of the infiltrated scar revealed definite evidence of carcinoma. The pathologist was of the opinion that the mother tissue was that of the gallbladder. The liver and bile passages showed no evidence of carcinoma. We cite this instance, because it shows the necessity of the histologic study of scars, and also because it emphasizes that the malignant process, though in

38. From the Stomach Study Group of the Michael Reese Hospital.

39. Nagel, G. W.: Unusual Conditions in the Duodenum and Their Significance, Arch. Surg. **11**:529 (Oct.) 1925.

the scar, may not be primary in the duodenum. We likewise direct attention to the fact that resection is the method of treatment for duodenal ulcer in relatively few clinics. We are of the opinion that if this procedure is followed and a greater number of scars of duodenal ulcers are subjected to histologic study, the incidence of duodenal carcinoma may be found to be greater.

In like manner, we question whether a certain number of cases that are diagnosed at operation as carcinoma of the head of the pancreas and that are not followed by later careful histologic study may not have their origin as a primary duodenal carcinoma. It occurs to us that in well advanced cases of primary duodenal carcinoma in which it is so difficult to determine the primary focus it is conceivable that the traditional rarity of a duodenal carcinoma directs the examiner's mind away from the duodenum, and therefore the diagnosis is that of a primary lesion in the adjacent structures, such as the pancreas, the papilla or the gallbladder.

TREATMENT

Medical treatment can be of little value except so far as it may be directed toward symptomatic relief. As metastases do not appear until late, surgical intervention is advocated as the method of predilection. The type of operation, however, will depend on the presence or absence of jaundice or metastases. In instances without the aforementioned complications, wide excision is recommended. Syme [23] resected a carcinoma of the third portion of the duodenum; the patient was in good condition when seen one month later. Pauchet and Luquet [22] resected the fourth portion of the duodenum for carcinoma. This patient was able to resume his daily labors a short time later. Dewis and Morse [24] reported a case in which a posterior gastrojejunostomy was performed for suspected nonmalignant duodenal ulcer. Two and a half months later, the ulcer was considered malignant, and a wide resection was performed. The patient was alive and well one year and five and a half months after the first admission. With the development of metastases, or if the general condition is too poor to permit resection, a palliative posterior gastro-enterostomy should be performed. When duodenal carcinomas are associated with jaundice, such as in the periampullary form, they are best treated by preliminary cholecystogastrostomy, duodenostomy or enterostomy, followed later by either posterior gastro-enterostomy or resection, depending on the exigencies of the cases.

For discussion and descriptions of the technic involved in surgical intervention in the periampullary form, the excellent papers of

Halsted,[40] Mayo,[41] Kausch,[42] Lewis,[43] Abell [44] and Cohen and Colp [45] are mentioned.

CONCLUSIONS

Four cases of primary carcinoma of the duodenum are reported. Emphasis is placed on the difficulty of clinical recognition and of the necessity of carefully studying, clinically as well as histologically, all cases of duodenal stenosis. A critical analysis may reveal a greater incidence of primary duodenal carcinomas.

55 East Washington Street.

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40. Halsted, W. S.: Contributions to the Surgery of the Bile Passages, Especially of the Common Bile Duct, Boston M. & S. J. **141**:645, 1899.

41. Mayo, W. J.: Cancer of the Common Bile Duct: Report of a Case of Carcinoma of the Duodenal End of the Common Duct with Successful Excision, St. Paul M. J. **3**:374, 1901.

42. Kausch, W.: Die Resektion des mittleren Duodenum: Eine typische Operation, Zentralbl. f. Chir. **36**:1350, 1909; Das Karzinon der Papilla duodeni und seine Radikale: Eutfierung, Beitr. z. klin. Chir. **78**:439 (May) 1912.

43. Lewis, R. N.: Cancer of the Ampulla of Vater, Surg. Gynec. Obst. **32**:543 (June) 1921.

44. Abell, I.: Carcinoma of the Papilla of Vater, South. M. J. **17**:24 (Jan.) 1924.

45. Cohen, I., and Colp, R.: Cancer of Periampullary Region of Duodenum, Surg. Gynec. Obst. **45**:332 (Sept.) 1927.

ACUTE ISOLATED MYOCARDITIS

WITH REPORT OF A CASE *

CLARENCE E. DE LA CHAPELLE, M.D.
AND
IRVING GRAEF, M.D.
NEW YORK

Recently, Scott and Saphir [1] reported two cases of acute isolated myocarditis, which were the first to be recorded in the American literature. They mentioned the reports of thirty-six other cases with postmortem observations recorded in the Continental literature since 1888, when Steffen [2] described two cases of acute myocarditis which probably fall into this classification. Fiedler,[3] however, in 1890 was the first to give a clear description of the disease, and it is his name that has served as an eponym since.

There are many synonyms in use in labeling this type of lesion. A few of the terms used by previous authors are "interstitial," "circumscribed," "diffuse," "isolated," "idiopathic" and "primary," singly or in combination. The terms refer to an inflammatory lesion of the myocardium alone, which is associated with a distinctive clinical and pathologic picture.

Sellentin [4] was the first to name the disease isolated myocarditis because, as a rule, changes are not found in other parts of the heart or in other organs.

It has been noted by practically all authors that the outstanding clinical feature is progressive myocardial insufficiency which may be rapid or gradual. The striking feature in most of the cases has been the lack of association with antecedent infectious diseases, valvular heart disease or hypertension.

Thirty of the previously recorded cases were tabulated by Scott and Saphir.[1] Of these, ten occurred in males and thirteen in females; the authors added their two cases to the male group. Information as to the

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* From the Third (New York University) Medical Division and the Pathological Laboratories, Bellevue Hospital.

1. Scott, R. W., and Saphir, Otto.: Acute Isolated Myocarditis, Am. Heart J. **5**:129 (Dec.) 1929.

2. Steffen, A.: Zur akuten Myokarditis, Jahrb. f. Kinderh. **27**:223, 1888.

3. Fiedler, A.: Ueber akute interstitielle Myokarditis, Centralbl. f. inn. Med. **21**:212, 1900.

4. Sellentin, L.: Akute isolierte interstitielle Myokarditis, Ztschr. f. klin. Med. **56**:298, 1904.

sex of the other seven patients was not available. Incidence as to age in their table indicates a distribution from the first to the eighth decades. Ten, or more than one third of all of the cases previously recorded with data on the age of the patients (total twenty-eight, including the two cases reported by Scott and Saphir), occurred in the third decade.

Evidence of the common infections recognized as the usual cause of heart disease was lacking in most of the cases, and a clearly defined etiologic agent has not been demonstrated to the present time. However, some authors associated the changes found with certain infections, e. g., influenza, carbuncles, gonorrheal urethritis, pneumonia, infected wounds, cellulitis and rheumatism. Two cases were associated with burns.

Necropsy observations in most of the cases have revealed enlargement of the heart, with marked dilatation of the chambers. The muscle of the heart has been variously described as pale, swollen and soft, sometimes as friable, with irregular streaks and spots varying in size and color scattered throughout. An observation common to all has been the absence of pericardial and endocardial lesions. Intracardiac mural thrombi have been found frequently.

Gallavardin[5] recently added another case to the literature. He observed progressive myocardial insufficiency, associated with idiopathic cardiac enlargement without signs of valvular disease, in a white woman, 37 years old. The patient's history was not important. The clinical course lasted six months, and the diagnosis of subacute primary myocarditis was made before death. At necropsy the heart was enlarged, more dilated than hypertrophied, and weighed 420 Gm. On section, there were characteristic changes with considerable fibrosis confined to the wall of the left ventricle. Histologic changes were similar to the recorded observations.

The first histologic description was made by Schmorl,[6] who examined Fiedler's cases. Microscopically, all authors gave the description of diffuse infiltration of the myocardium with cellular elements of different types. Some noted chiefly polymorphonuclear leukocytes, occasional round cells and a few eosinophils. In his case, Saltykow[7] described the infiltration as consisting of polymorphonuclear leukocytes, lymphocytes, fibroblasts, plasma cells, mast cells, wandering endothelial cells and eosinophils, as well as cells that he thought were degenerating forms of muscle cells. The latter were also found forming giant cells.

5. Gallavardin, L., and Gravier, L.: Un nouveau cas de myocardite subaiguë primitive à lésions interstitielles, Arch. d. mal. du cœur **22**:379, 1929.

6. Schmorl, L., in discussion of Aschoff, L.: Verhandl. d. deutsch. path. Gesellsch. **8**:46, 1904.

7. Saltykow, S.: Ueber diffuse Myokarditis, Virchows Arch. f. path. Anat. **182**:1, 1905.

Aschoff [8] recorded a case that he felt was of rheumatic origin combined with some other agent. Aschoff's case showed eosinophils, plasma cells, lymphocytes and a few fibroblasts, with slight necrosis of the muscle fibers. Other authors described other histologic pictures. All agreed that the primary changes are in the interstitial tissues, the parenchyma being inconstantly involved. Gallavardin [5] called attention to the possibility that the interstitial lesions are secondary to parenchymal necrosis, and indicated that the term "interstitial" refers to the end-stage of the lesion.

The following case is reported to add another example of what appears to be Fiedler's myocarditis to the small group already recorded.

REPORT OF CASE

History.—A. M., a white man, aged 21, born in Argentina, a laborer, was admitted to Bellevue Hospital, Third (New York University) Medical Division, on Jan. 25, 1930, complaining of pain in the chest and dyspnea of about two weeks' duration. His family history was irrelevant. He did not recall having had any of the diseases of childhood. He had had frequent colds, but at no time had he had polyarthritis. He said that he had not had venereal disease.

In May, 1929, while riding a bicycle, the patient suddenly and without premonitory symptoms fell (unconscious?). He was removed to a hospital, where it was found that he had hemiplegia. A diagnosis of hysteria was also made. In this hospital, Wassermann tests of the blood and spinal fluid were reported to be negative; the colloidal gold curve was also negative. Other laboratory tests also gave negative results. On discharge four days later, he was able to use his left arm and leg to a slight extent. His condition improved gradually, and by August he was practically normal, except for slight weakness of the left hand.

About Jan. 1, 1930, the patient began to cough; he consulted a physician, who gave him medicine and instructions to return in a week. The cough grew progressively worse. During the second week of the illness, he expectorated bloody sputum and began to experience pain in the lower right side of the chest. At this time he noticed shortness of breath on slight exertion. He returned to his physician, who strapped his chest. The cough, blood-tinged sputum, shortness of breath, pain in the chest and weakness persisted, and the patient went to bed. After a week the patient entered Bellevue Hospital because of continued dyspnea and pain in the chest. At the time of admission, the productive cough had practically disappeared. He had not felt feverish, lost weight, sustained a chill or experienced night sweats at any time during his illness, but he had noticed swelling of his feet during the week previous to admission.

Examination.—The patient appeared to be chronically ill, but well nourished. He was slightly dyspneic and orthopneic, and he had a café-au-lait color. There was cyanosis of the lips and finger tips. His pupils reacted to light and in accommodation. No petechiae were seen in the conjunctivae; the sclerae were icteroid; the fundi oculi presented the slate appearance of cyanosis; the retinal vessels were normal, and there was no evidence of hemorrhages or exudates. The pharynx and tonsils were hyperemic, but no pus could be expressed from the latter. The

8. Aschoff, L.: Zur Myokarditisfrage, Verhandl. d. deutsch. path. Gesellsch. **8**:46, 1904.

tonsillar lymph nodes were palpable on the right side. The teeth were in fair condition. The thyroid was not visible or palpable. There was no clubbing of the fingers.

Examination of the heart revealed pulsating veins in the neck; one of the superficial veins of the left arm could be seen to pulsate. The apical beat of the heart was visible and palpable in the sixth space, 14 cm. from the median line, which point was at the anterior axillary line. A 2 meter roentgenogram of the heart, taken five days after admission, showed marked enlargement in the transverse and long diameters. The first sound at the apex of the heart was of poor muscular quality; the sounds at the base were faintly audible. The rhythm was regular; the rate was 92 a minute, and the radial pulse was small. The systolic blood pressure was 105 mm., the diastolic, 82 mm.

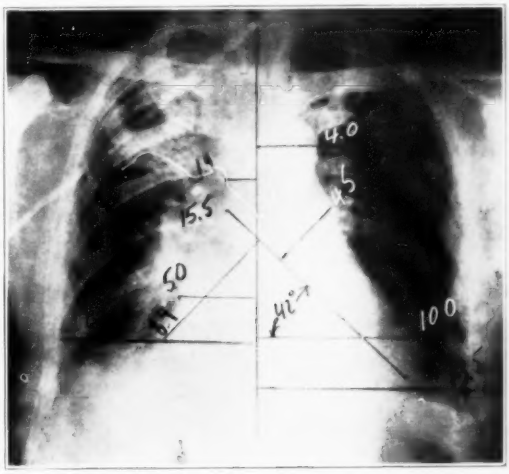

Fig. 1.—Roentgenogram (2 meters) of the heart taken nine days before death, showing marked enlargement of the cardiac outline.

The respiratory rate was 32 a minute. There were signs of fluid over the area of the lower lobe of the right lung, with crepitant and subcrepitant râles and dulness above the eighth rib posteriorly. The edge of the liver was palpable 3 cm. below the costal margin; it was tender, but did not pulsate. The spleen was not palpable. There was no evidence of ascites. Both lower extremities presented slight edema. The superficial and deep reflexes were active, and there were no abnormal reflexes.

On admission, examination of the blood showed: leukocytes, 10,400; polymorphonuclears, 79 per cent; lymphocytes, 20 per cent; transitionals, 1 per cent; red cells, 3,700,000, and hemoglobin, 70 per cent. Another leukocyte count, taken four days later, showed 17,200 leukocytes, with 92 per cent polymorphonuclears and 8 per cent lymphocytes. The Wassermann reaction of the blood was negative. Blood cultures taken on two different occasions yielded no growth. The systolic blood pressure never exceeded 112 mm.; the diastolic pressure ranged between

82 and 92 mm. Four electrocardiograms, taken on different days during the last week, revealed prolongation of the P-R interval (from 0.20 to 0.24); there was a complete intraventricular block; low voltage in all three leads and normal sinus rhythm. Examination of the sputum revealed an unclassified pneumococcus. On admission, the urine was normal; subsequent urinalysis revealed a slight albuminuria and the appearance of numerous hyaline and finely granular casts; an occasional red blood cell was found on one occasion the day before death. Chemical analysis of the blood, performed two days after admission, showed: nonprotein nitrogen, 64 mg., and sugar, 119 mg. per hundred cubic centimeters. Three days before death, the nonprotein nitrogen was 100 mg. and the creatinine 4.7 mg. per hundred cubic centimeters.

Clinical Course.—The temperature ranged between 98 and 100 F., the pulse rate between 68 and 100 a minute. Thoracentesis was performed two days after admission and yielded 80 cc. of clear straw-colored fluid, with a specific gravity of

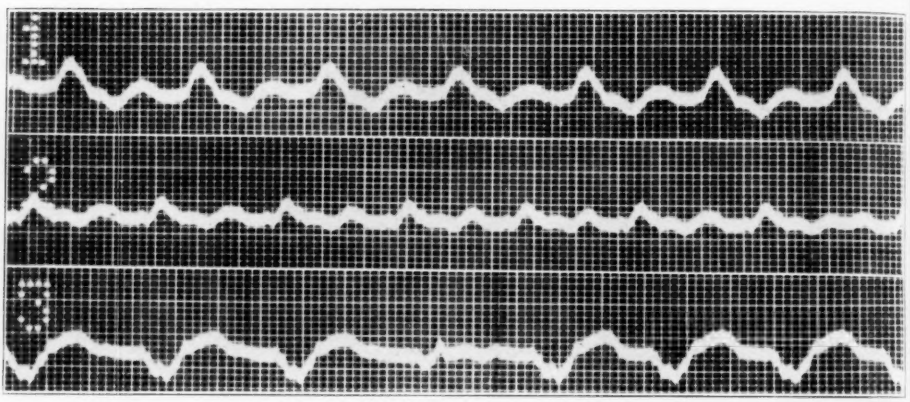

Fig. 2.—One of four similar electrocardiograms obtained between January 30 and February 5. First stage A-V block; complete intraventricular block; string resistance, 4,000 ohms; resistance of patient, 2,000 ohms; rate, 90; P-R interval, 0.20; QRS, 0.18; T_1 and T_2 inverted, and sinus arrhythmia.

1.008. The cell count was 1,940, the differential count being comprised chiefly of lymphocytes and endothelial cells. No tubercle bacilli were found. The signs in the lower lobe of the right lung persisted. A roentgenogram of the lungs showed irregular consolidation in this field.

The patient progressively gained weight, with an increasing edema of the lower extremities and the left arm and hand. Facial edema became marked about four days before death. There was no change in the cardiac observations. The liver became progressively enlarged and palpable 8 cm. below the costal margin in the midclavicular line, and it was tender. Cyanosis, which was of a fairly marked degree, was intermittent. During the last few days, as the congestive heart failure became more marked, slight icterus, oliguria, Cheyne-Stokes respirations and stupor supervened, so that the patient died twelve days after admission, presenting a picture of heart failure and uremia.

The final clinical diagnosis was cardiac disease:[9] (*a*) etiology—unknown, active; (*b*) anatomy—enlarged heart; (*c*) physiology—sinus rhythm with intraventricular block (complete bundle branch) and auriculoventricular block, first stage; (*d*) functional—class III.

Pathologic Report.—Necropsy was performed about ten hours after death, the incision being limited to the abdomen. The body was that of an adult white man, weighing 68 Kg., 177 cm. in height, well nourished and well developed. Except for moderate pitting edema of the legs, trunk and left arm and slight icterus of the skin and sclerae, external examination gave negative results. On section, the panniculus was yellow and of normal thickness; the muscles were pale brown.

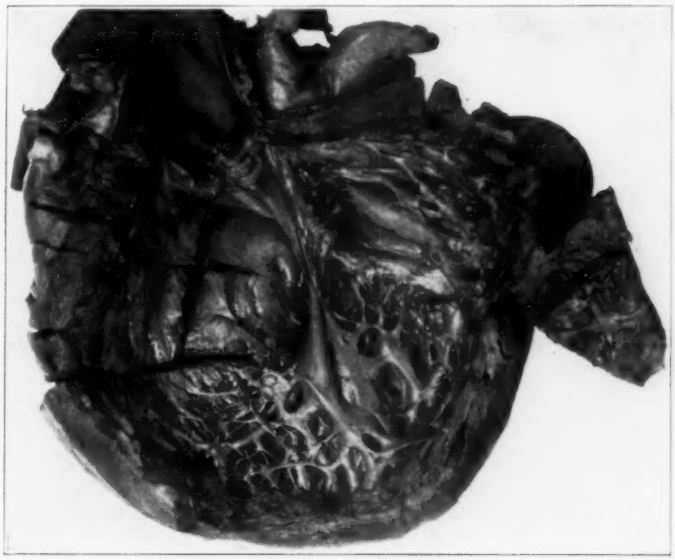

Fig. 3.—The opened heart, showing marked dilatation of the left ventricle and the mural thrombus at the apex. Note the normal mitral and aortic valves.

Examination of the serous cavities showed that the peritoneal cavity contained about 500 cc. of clear, straw-colored fluid. Each pleural cavity contained about 300 cc. of clear fluid. The pericardial sac contained about 75 cc. of clear fluid. Otherwise, the serous sacs were intact.

The heart was large, weighing 600 Gm. Its external measurements were 16 by 13 by 9 cm. It was so soft and flabby as to mushroom over the supporting hand. All of the chambers were markedly dilated. The papillary muscles of both ventricles were flattened. The mitral valve and its chordae tendineae were

9. This diagnosis conforms to the nomenclature for cardiac diagnosis recommended by the American Heart Association (Am. Heart J. **2**:202, 1926-1927).

normal. The orifice of the valve measured 10 cm. in circumference. The aortic orifice measured 6 cm. in circumference; the cusps were normal. The orifice of the tricuspid valve measured 11.5 cm. in circumference; the valve and its chordae tendineae were normal. The pulmonary orifice measured 6 cm. in circumference; its cusps were normal. The myocardium of the left ventricle measured 18 mm. in thickness at the base of the ventricle, 10 mm. near the apex and from 2 to 3

Fig. 4.—Low power photomicrograph of a section of the left ventricle. Note the hypertrophied nuclei and muscle fibers, and the diffuse and patchy cellular infiltration by small round cells. Hematoxylin and eosin stain.

mm. at the apex. The right ventricle measured 6 mm. in thickness at the base and 3 mm. at the apex. The epicardium was normal, except for a few pinhead-sized, smooth, glistening points of thickening over the right auricular appendage. The endocardium was intact throughout, except at the apex of the left ventricle, where a firm, grayish-red thrombus was found attached to the endocardium. The right auricular appendage was filled by a similar thrombus. On section, the myo-

cardium, particularly that of the left ventricle, was remarkably altered, brown and brownish-yellow streaks being scattered throughout; nearby were seen irregular bands of gray and grayish-yellow firmer tissue. On section, the linear markings of the muscle bundles were barely visible. The coronary orifices and arteries were normal.

Both lungs were heavier than normal; the pleural surfaces were smooth. The cut surfaces were reddish-blue and oozed frothy sero-sanguineous fluid; they were otherwise normal.

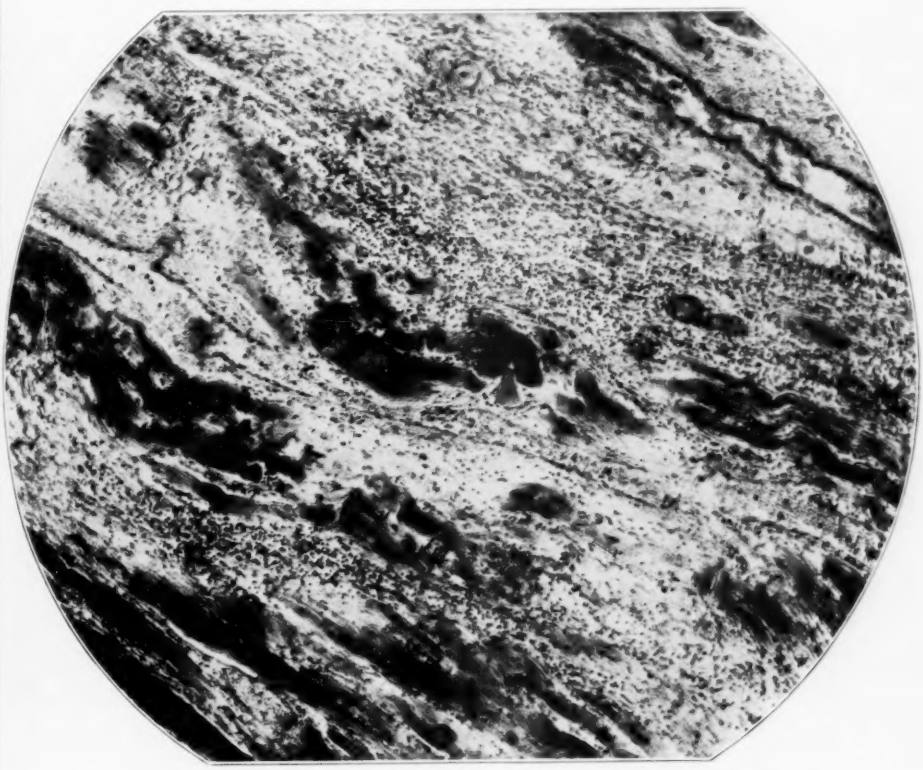

Fig. 5.—Low power photomicrograph of a section of the left ventricle close to the A-V sulcus posteriorly. Note the replacement of the muscle fibers of the heart by cellular infiltration. Hematoxylin and eosin stain.

The liver weighed 1,300 Gm. The capsule was smooth. The cut surface was firm, showing the markings of chronic passive congestion which gave the organ a nutmeg appearance. The gallbladder and biliary passages were normal.

The spleen was normal in size and shape, weighing 220 Gm. On section, the pulp was firm and red, and the follicles were fairly prominent.

The kidneys were somewhat enlarged, weighing 420 Gm. together. The capsules stripped easily, leaving a smooth surface. On section, they were normal, except for slight hyperemia and one small, gray, apparently healed infarct in the right kidney.

The pancreas, suprarenal glands, bladder, prostate and testes appeared normal.

Microscopic Observations.—Sections were taken from both ventricles, both auricles, the auricular appendages, valves, papillary muscles, aorta and pulmonary artery of the heart. The following stains were used: hematoxylin-eosin, van

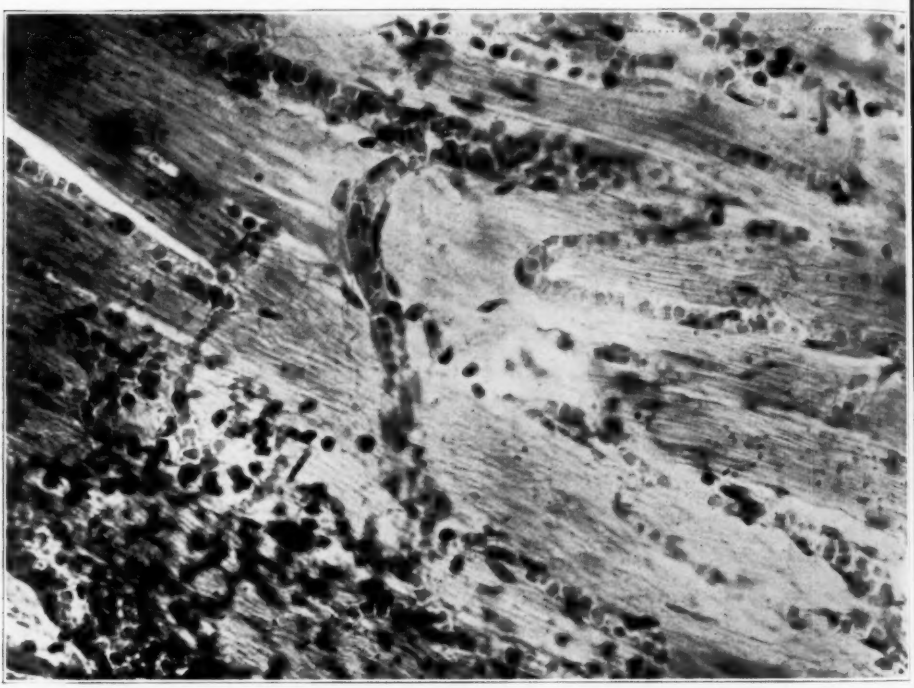

Fig. 6.—High power photomicrograph of a section of the right ventricle, showing new capillaries traversing the muscle fibers. Note the marked hyperemia. Hematoxylin and eosin stain.

Gieson, Mallory's connective tissue stain, Weigert's elastic tissue stain, sudan III, nile blue, Gram-Weigert, methyl violet, Unna-Pappenheim, Levaditi and Warthin-Starry.

Sections from various portions of both ventricles revealed marked hypertrophy of the nuclei and fibers of the muscles, both of which were many times larger than in normal circumstances. The interstitial connective tissue was increased in amount. The coronary arteries and arterioles were apparently normal. Newly formed blood vessels were abundant and injected. In places they were seen growing into and between muscle bundles and fibers. No lipochrome pigment was seen.

The lesion noted was widely distributed and more marked in the myocardium of the left ventricle. Areas of considerable dimension were found consisting of degenerated, edematous muscle fibers and nuclei, infiltrated by large numbers of lymphocytes, endothelial cells, fibroblasts and newly formed blood vessels. These areas were irregular in outline and poorly demarcated, and they did not present a constant picture, the several elements varying in number and location. In some places there was an abundance of young connective tissue cells with a few lympho-

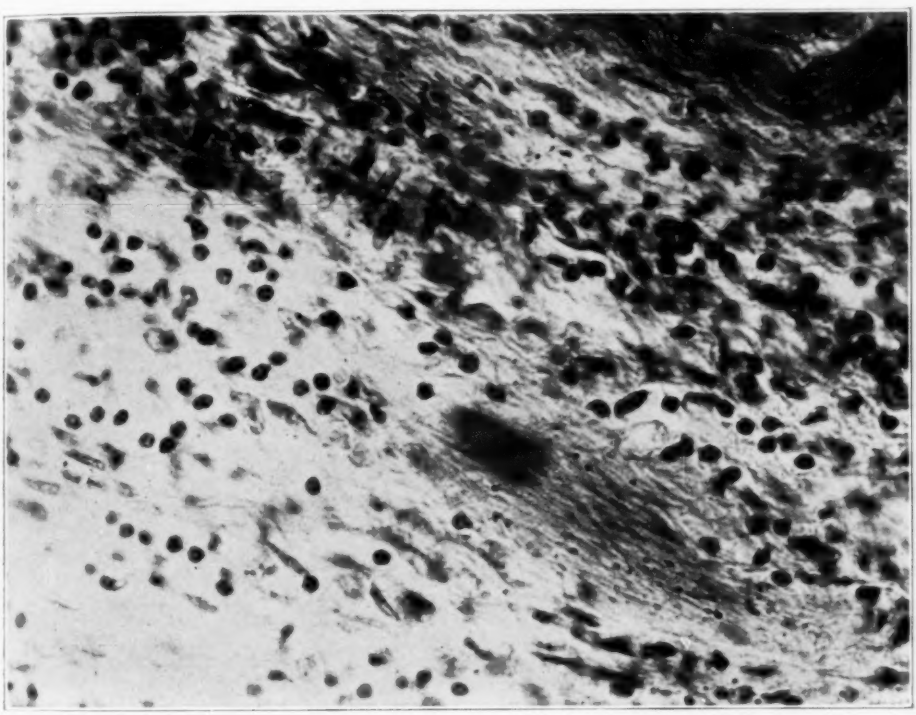

Fig. 7.—High power photomicrograph of a section of the left ventricle, showing diffuse cellular infiltration, notably of the round cells, occasionally by cells of endothelial type, and replacement of the muscle fibers of the heart. Hematoxylin and eosin stain.

cytes and an occasional plasma cell; in other places focal collections of lymphocytes, a few plasma cells and large endothelial cells were found in and around edematous muscle fibers. Some of the endothelial cells presented sharply outlined nuclei, and in their cytoplasm a fine granular pigment was occasionally seen. No giant cells or Aschoff bodies were found in any of the sections. One small coronary artery was found to contain a small nonoccluding parietal thrombus composed of fibrin, in the meshes of which a few leukocytes could be seen. Near the well marked areas of inflammatory reaction small focal areas of muscle necrosis

were encountered with no surrounding inflammatory reaction. The cross striations of the muscle fibers were normal, except in the areas of degeneration. Fat was not markedly increased in amount; with the sudan III stain it could be seen in fine droplets in most of the myocardial fibers. Sections stained by the van Gieson and Mallory connective tissue methods showed scattered foci of fibrous connective tissue. These were chiefly interstitial. With these stains the interstitial elements

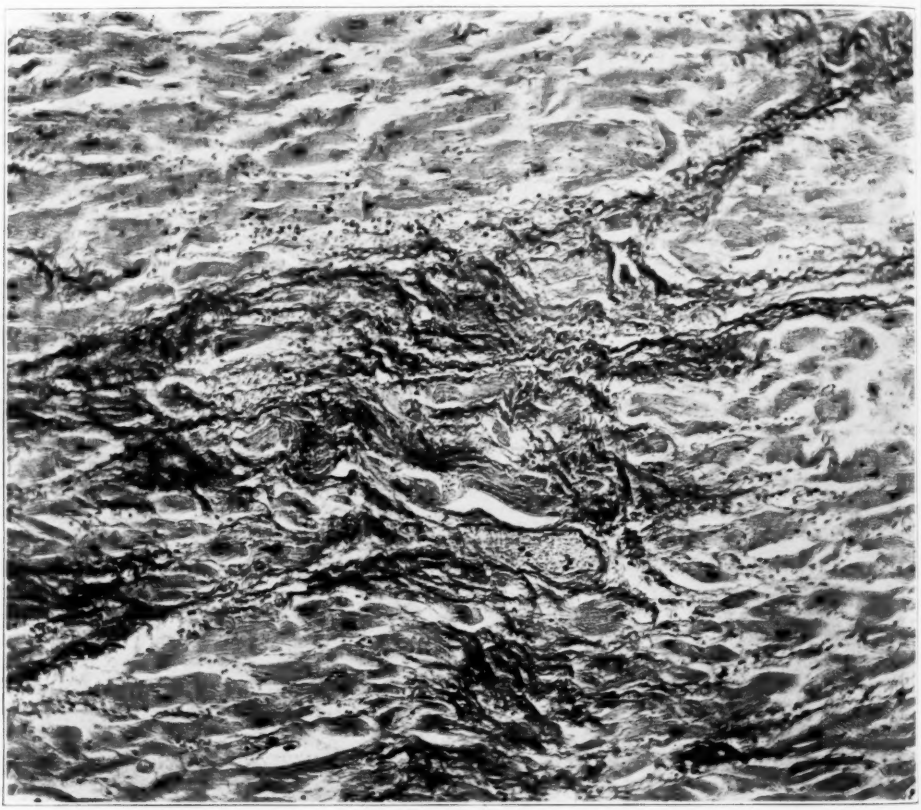

Fig. 8.—Low power photomicrograph of the myocardium of the left ventricle. Note the diffuse intrafascicular increase of fibrillary connective tissue. Van Gieson stain.

in the areas of degeneration of the muscle were seen as fine fibrillar bands with no intervening stained sarcoplasm. Polymorphonuclear leukocytes and eosinophils were scarce. No areas of hemorrhage were seen.

A section from the apex of the left ventricle revealed a fairly advanced organizing process, involving the endocardial thrombus and the adjacent muscle. Sections of the valves and the endocardium revealed normal structures except at the

apex, as noted. Sections of the aorta and pulmonary artery showed no changes. The stains for amyloid, bacteria and spirochetes yielded negative results.

Sections of the lungs revealed numerous cells indicative of heart failure, occasional areas of edema and marked hyperemia of the small vessels. Sections of patchy atelectasis could be seen.

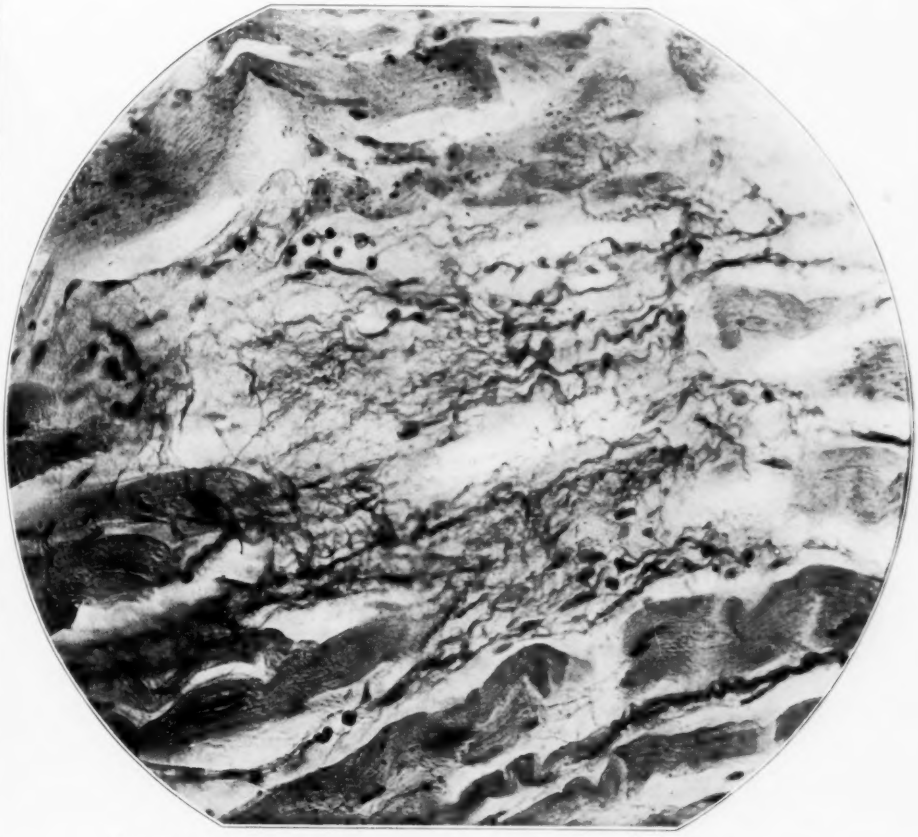

Fig. 9.—High power photomicrograph of a section of the left ventricle. Note the loose fibrillary connective tissue in an area of necrosis with no cellular reaction. Van Gieson stain.

The central veins of the liver and the adjacent sinusoids were choked with blood elements compressing the cords of the liver. In some of the lobules central necrosis was seen. Considerable bile pigment was seen in the liver cells.

The capsule of the spleen was thin. The splenic sinuses were markedly congested. The follicles were hyperplastic. The arterioles showed no changes.

Most of the glomeruli in the kidneys were normal. An occasional glomerulus was seen with swollen lining cells in Bowman's capsule. The tubules were fairly

well preserved. Many of the proximal convoluted tubules showed marked cloudy swelling. The lumina contained epithelial and hyaline casts. Section through the area of infarction revealed replacement of the parenchyma by dense acellular connective tissue. The edges were sharply defined.

The pathologic diagnosis was: subacute productive myocarditis; hypertrophy and dilatation of the heart; mural thrombi of the left ventricle and the right

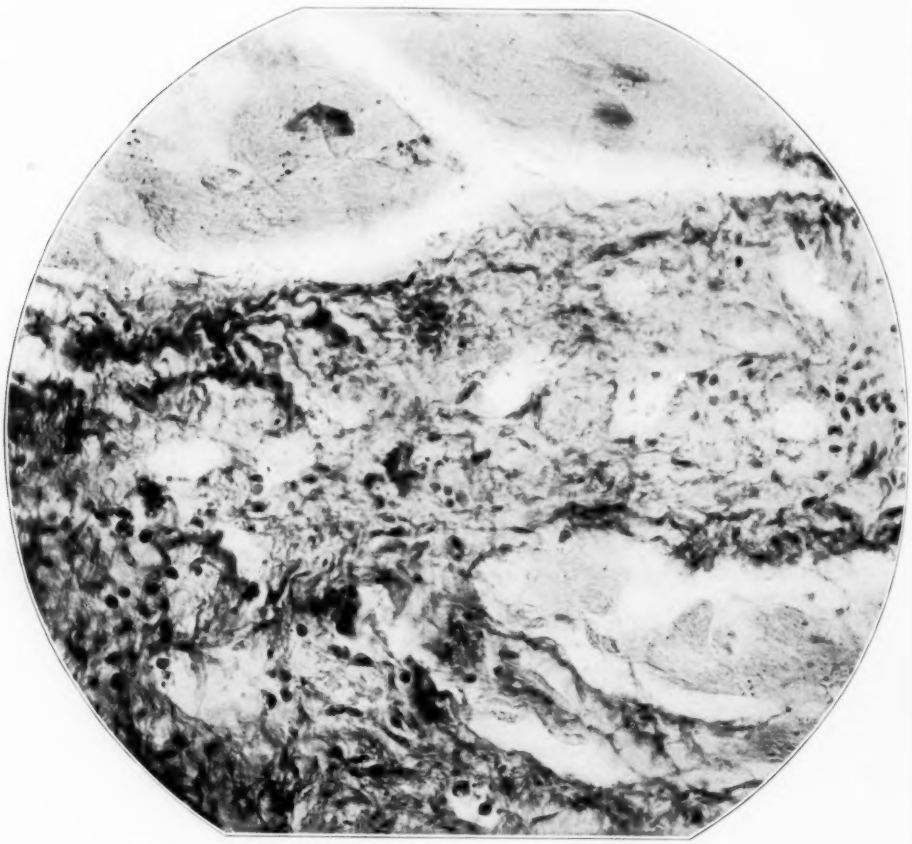

Fig. 10.—High power photomicrograph of the myocardium of the left ventricle. Note the increase in connective tissue, which is more dense than in figure 9, extending between and replacing muscle bundles; note, too, the moderate round cell infiltration. Van Gieson stain.

auricular appendage; healed infarct of the right kidney; chronic passive hyperemia of the lungs, liver, spleen and kidneys; follicular hyperplasia of the spleen; cloudy swelling of the kidneys; generalized edema; ascites and icterus.

COMMENT

Progressive heart failure was the outstanding clinical feature in our case. This is in accord with the observations of previous authors.

Careful search of the history in this case for an etiologic factor was unavailing. There was no history of any of the well known infectious diseases, including rheumatic fever, diphtheria, scarlet fever, syphilis or tuberculosis; nor were we able by any means available to demonstrate an etiologic agent. Two blood cultures taken during the patient's stay in the hospital were sterile.

The exact onset of the disease in this case is doubtful. The embolic phenomena noted during life and the evidence for the same found at necropsy are particularly noteworthy and possibly give a clue to the onset and duration of the lesion.

In 1901, Josserand and Gallavardin[10] recorded three cases of Fiedler's myocarditis with careful clinical and pathologic studies. Their cases occurred in young men in the third decade. In each case, they emphasized the abrupt onset with embolic manifestations, pulmonary or cerebral, followed by progressive myocardial failure.

In our case, the cerebral accident about eight and one-half months before death, the healed infarct in the kidney and the probable pulmonary infarct about six weeks before death suggest that the intracardiac thrombi were present for some time. During the patient's first hospitalization, it was noted further that the heart was enlarged, the apex being 1 cm. to the left of the midclavicular line in the fifth interspace. Moreover, the heart weighed 600 Gm. and exhibited marked hypertrophy, lending further support to the contention that the disease had existed for a period of months.

Of considerable clinical interest are the data obtained by electrocardiography, which gave further evidence of the extensive distribution of the lesion, i. e., first stage auriculoventricular block (P-R interval, from 0.20 to 0.24) and complete intraventricular block.

The gross and microscopic observations demonstrate the distribution of the lesion. The diffuse and focal cellular infiltration consisting chiefly of lymphocytes, the new formation of blood vessels and connective tissue, involving both the interstitium and the parenchyma, the well marked deposits of organized connective tissue and the focal areas of necrosis account for the progressive circulatory failure. Careful microscopic studies have not been made of the conducting tissue. There were no vascular, perivascular or myocardial lesions suggesting rheumatic infection, and no Aschoff bodies were found.

10. Josserand, E., and Gallavardin, L.: De l'asystolie progressive des jeunes sujets par myocarditis subaiguë primitive, Arch. gén. de méd. **78**:513 and 684, 1901.

The necropsy observations adequately account for the clinical course. The etiology in our case remains obscure. Whether or not the lesion was an atypical rheumatic inflammatory reaction cannot be answered. Aschoff [8] felt that the lesions in his case could not be explained or described as rheumatic alone. He suggested that some other etiologic factor was combined or superimposed, possibly an infection of cryptogenic origin. We believe, with Scott and Saphir, that to regard these cases as rheumatic would not aid in clarifying the knowledge of their pathogenesis.

SUMMARY

A case of so-called isolated myocarditis of unknown etiology is reported.

The clinical and necropsy observations are compared with those in previously recorded cases.

Electrocardiograms showing evidence of severe impairment of conduction are noted for the first time in connection with this disease.

IV. CORONARY SINUS RHYTHM

RHYTHM SUBSEQUENT TO DESTRUCTION BY RADON OF THE SINO-AURICULAR NODES IN DOGS *

MILTON C. BORMAN, M.D.
MILWAUKEE

AND

WALTER J. MEEK, PH.D.
MADISON, WIS.

It has usually been assumed that when the sino-auricular nodes in the hearts of dogs have been completely destroyed the auriculoventricular node, particularly its coronary sinus portion, becomes the pacemaker or the initiatory mechanism. Eyster and Meek [1] reported in such cases a decreased p-r interval and a decreased cardiac rate. Borman,[2] however, obtained normal electrocardiograms from dogs in which the sino-auricular nodes had been destroyed by radon. Therefore, it was our primary object in this study to determine the exact site of the initiation of the impulse in a larger series of dogs in which complete destruction of the sino-auricular nodes was similarly produced by radon.

METHOD

In a series of thirty dogs, the sino-auricular nodes were aseptically exposed. The only modification of the previously described technic [2] consisted in the use of capillary tubes containing radon which were either inserted subepicardially by means of a right angle applicator, or as in the later experiments, by tying the radon seed with silk sutures to the epicardium overlying the sino-auricular node. By careful asepsis, a subcuticular closing suture being used, practically primary closure of the wound of the chest was obtained. The duration of the operation varied from twenty to forty minutes. After an interval of several weeks or months, during which electrocardiograms were taken, the animals were again anesthetized, tracheotomy performed, the internal mammary vessels ligated and the sternum and portion of the attached ribs resected, exposing the pericardial sac. The latter was incised and the margins sewed to the edges of the wound. Auricular systole was recorded on the electrocardiographic record by means of the transmission of air and a recording tambour. Fine silk sutures were inserted over the head of the sino-auricular node and the body of the right atrium, catching only a tiny portion of the epicardium. By means of the long ends of these sutures, a woolen

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* From the Department of Physiology, University of Wisconsin Medical School, Madison, Wis., and the Sacred Heart Sanitarium, Milwaukee.

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2. Borman, Milton C.: Destruction of the Sino-Auricular Node in Dogs' Hearts by Radon, Am. Heart J. **3**:208, 1927.

strand moistened in physiologic solution of sodium chloride was tied to each suture. The ends of the sutures and woolen strands were neatly and closely cut, so that contact with the epicardial surface was obtained at a very small point. Each of the woolen strands passed upward into a glass tube, the lower end of which was packed lightly but firmly enough to avoid leakage with the wool soaked in physiologic solution of sodium chloride. The remaining portion of the glass tube was filled with a saturated solution of zinc sulphate. The leads of an electrocardiograph were connected to the electrodes by a small zinc rod freshly cleansed with sulphuric acid, and dipped in mercury. By changing these zinc rods, which were dipped in the upper end of the glass tubes containing the solution of zinc sulphate, leads could be quickly interchanged, furnishing a check in the determinations of negativity. If the initial deflection was an upstroke when the

TABLE 1.—*Electrocardiograms Before and After Operation on Dog 8*

No.	Condition	p-r Interval in Seconds	Cardiac Rate	Abnormalities
1	Normal	0.11-0.12	90	
2	47 minutes after administration of 1 grain of morphine sulphate subcutaneously	0.11-0.12	100	
3	53 minutes after administration of morphine sulphate and 4 minutes after injection of 0.001 Gm. of atropine sulphate	0.12-0.14	120	
4	10 hours after 2.09 millicuries of radon implanted	0.09-0.11	75	
5	23 hours after operation	0.09-0.10	60	
6	33 hours after operation	0.08-0.10	84	p waves barely visible
7	2 days after operation	0.10-0.11	100	
8	3 days after operation	0.10-0.12	108	
9	5 days after operation	0.11-0.13	70	Cycles of sino-auricular block
10	6 days after operation	0.13-0.14	60	Cycles of sino-auricular block
11	9 days after operation	0.10-0.12	100	Cycles of sino-auricular block; negative T^2 and T^3
12	17 days after operation	0.11-0.12	100	T in all leads negative
13	23 days after operation	0.10-0.12	100	T in all leads negative
14	38 days after operation	0.10-0.12	100	T in all leads negative
15	120 days after operation	0.10-0.12	100	Just prior to experiments on initial negativity
16	Body of right auricle initially negative when compared to sino-auricular node			
17	Coronary sinus initially negative when compared to sino-auricular node			
18	The same with leads inverted			
19	Body of right auricle negative when compared to sino-auricular node			
20	Coronary sinus initially negative when compared to body of right atrium			
21	The same with leads inverted			
22	Coronary sinus initially negative when compared to auriculoventricular node			
23	The same with leads inverted			
24	Auriculoventricular node initially negative when compared to sino-auricular node			
25	Normal electrocardiogram with indirect Einthoven leads; p-r interval 0.12; cardiac rate 130			

lead of the right wrist was over the sino-auricular node, the latter must be regarded as initially negative when compared to any other point. A glass rod curved almost at right angles, the lower end of which was packed with wool soaked in physiologic solution of sodium chloride, was placed behind the heart over the region of the coronary sinus. A fourth electrode, a slightly curved glass rod, was passed down the external jugular vein into the right side of the heart; the end was rotated medially so that it touched the base of the interauricular septum in the region of the auriculo-ventricular node. Thus at the termination of each experiment, the point of origin of the cardiac impulse was determined. Thereafter, the sino-auricular junctional tissues were fixed in formaldehyde; drawings were made of the gross anatomic changes, and the tissues were mounted in paraffin blocks. Duplicate sets of semiserial sections of each block were made and stained with hematoxylin and van Gieson's stains. Sections were stained from every 1 to 3 mm. of tissue.

DATA

Two series of animals were used in these experiments. In the 1927-1928 series, nine animals were used, while in the 1928-1929 series

TABLE 2.—*Summary Data on All Animals*

No.	Days Lived	Millicurie of Radon in Tube	Postoperative Changes in Electrocardiogram	Seat of Initiation of Impulse	Anatomic Observations
			1927-1928 Series		
5	120	0.99	p-r interval before operation, 0.14-0.14 second; thirty-ninth day after operation, 0.12-0.13 second; cycles of sino-auricular block; inverted T^2 and T^3	Sino-auricular node	Epicarditis, acute; no sino-auricular node seen
6	120	0.99	p-r interval before operation, 0.12 second; forty-fifth day after operation, 0.12-0.14 second	Coronary sinus	Grossly, nodular white scar on endocardial surface at head of node; histologically, necrosis and calcification; no sino-auricular node seen
8	120	2.09	p-r interval before operation, 0.11-0.12 second; thirty-eighth day after operation, 0.10-0.12 second; cycles of sino-auricular block	Coronary sinus	Grossly, round infiltrating scar at head of sino-auricular node; histologically, fatty change and hemorrhage; no sino-auricular node seen
			1928-1929 Series		
5	41	4.00	p-r interval before operation, 0.13-0.14 second; thirty-seventh day after operation, 0.11-0.12 second; on seventh day after operation, delayed conduction; seven cycles of nodal rhythm	Coronary sinus	Grossly, epicardial adhesions; hemorrhagic changes from sino-auricular junction caudally for 3 cm., 15 mm. in width; histologically, free hemorrhage, replacement of connective tissue; infiltration of round cells; no sino-auricular node seen
9	30	3.50	Before operation, inverted T^2; p-r interval, 0.12-0.15 second; twenty-sixth day after operation, inverted T^2; p-r interval, 0.14-0.16 second; decreased vagal tone; series of nodal cycles	Coronary sinus	Grossly, marked thickening 1 cm. above junction on both vena cava and on auricular side, and down 3 cm. below the junction; histologically, similar to changes in dog 5
13	20	4.30	Before operation, p-r interval, 0.14-0.15 second; fifteenth day after operation, p-r interval, 0.175-0.24 second; occasional sino-auricular block	Head of sino-auricular node	Grossly, white scar 15 mm. in length, 7 mm. in width, over the crista terminalis; endocardially, considerable hemorrhage; histologically, nutrient artery visible, surrounded by extensive coagulative necrosis and hemorrhage; no sino-auricular node seen
19	21	8.00	Before operation, p-r interval, 0.133-0.165 second; twentieth day after operation, p-r interval 0.09-0.11 second; on second day after operation, almost complete nodal rhythm; on fourth day, auriculo-ventricular block	Sino-auricular node	Grossly, white scar 2 cm. long and 6 mm. wide over crista, surrounded by area of hemorrhage, also visible endocardially; histologically, coagulative necrosis with hemorrhage in crista terminalis; no sino-auricular node seen

twenty-one animals were studied. In both series, preoperative and postoperative records showing the effects of morphine and atropine were obtained, which data may form the substance of a further report. The first three reports in table 2 were from the 1927-1928 series. The last four animals were from the later series. From the total group,

the data of only seven were included in table 2, because only in these were both initial negativity and histologic observations made. While histologic examinations were made in each experiment, many of the animals died from various causes or during the determination of initial negativity.

The following protocol of dog 8 illustrates the method used:

Dog 8 was operated on the day after a normal electrocardiographic study had been made, including tracings after the hypodermic administration of morphine and atropine. An implant containing 2.09 millicuries of radon was introduced beneath the epicardium overlying the sino-auricular node. At intervals during the following four months, electrocardiograms were obtained. The animal was prepared for direct electrocardiographic tracings in the manner previously described, and the point of initial negativity was noted by comparing the sino-auricular node to the body of the right auricle, the auriculoventricular node and the region of the coronary sinus, and vice versa. Examination of the junctional tissues revealed a large scar replacing all the tissue at the head of the crista terminalis. Histologically, no sino-auricular nodal tissue was seen. The tissue comprising the crista terminalis was replaced by scar, free hemorrhage and extensive fatty change.

Table 1 summarizes the electrocardiographic studies performed on dog 8. The combined data on all animals are summarized in table 2.

COMMENT

The use of radon (radium emanation) was first suggested to one of us by Dr. J. E. Sweet of Cornell Medical School several years ago when we were interested in a new method of destroying the sino-auricular node in the hearts [2] of dogs. In two of the animals studied at that time, cycles of nodal rhythm or ventricular escape were noted. Histologically, we were unable to find any evidence of sino-auricular nodal tissue in these two animals, although no such difficulty was experienced in others. It was therefore a natural assumption that a coronary sinus rhythm had probably developed in these two animals, although the electrocardiograms did not show a reduction in the p-r intervals or a decreased cardiac rate. The experiments conducted since that first report differed from the former ones in that larger doses of radon were used, and that at the termination of the long-time experiments Lewis' method of determining initial negativity was used to find the origin of the cardiac impulse.

In dog 5 (series of 1927-1928), cycles of sino-auricular block with inverted T^2 and T^3 waves were noted several months after the application of 0.99 millicuries of radon over the sino-auricular node. Although it was finally determined that the seat of the initiation of the impulse was in the sino-auricular node, histologically, no sino-auricular structure was found. This was probably due to faulty histologic technic, the sections being poorly cut and stained.

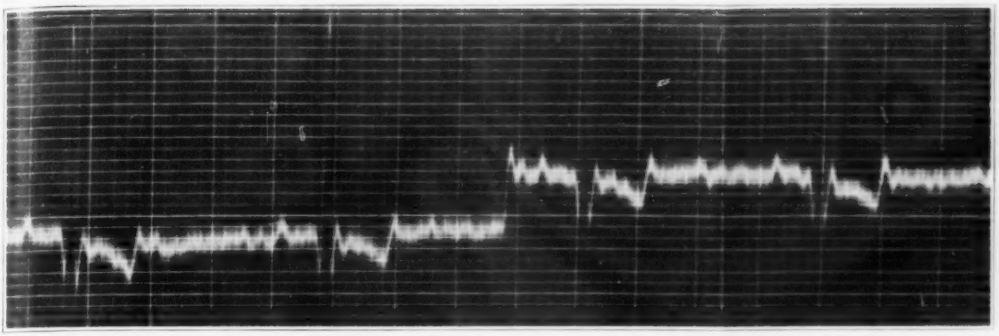

Fig. 1 (dog 3).—This dog was not included in the data because the animal died on the table during operation before determinations of the initial negativity could be completed. Preoperative record after the animal had received ½ grain of morphine sulphate subcutaneously. Result: normal rate and rhythm.

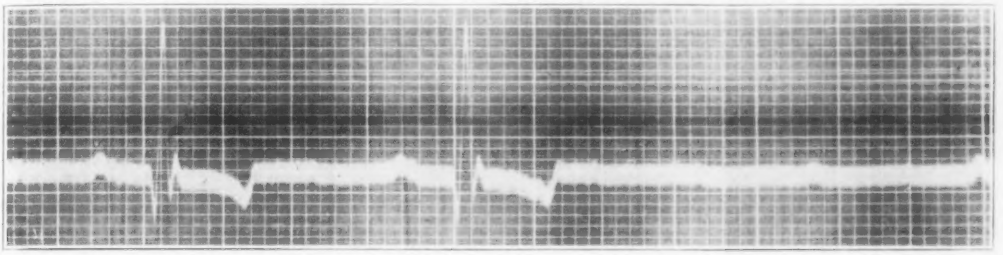

Fig. 2 (dog 3).—Postoperative record 119 days after constant exposure of the sino-auricular node to 1.31 millicuries of radon; immediately afterward ½ grain of morphine sulphate was injected subcutaneously. Result: occasional cycle of sino-auricular block with decreased rate.

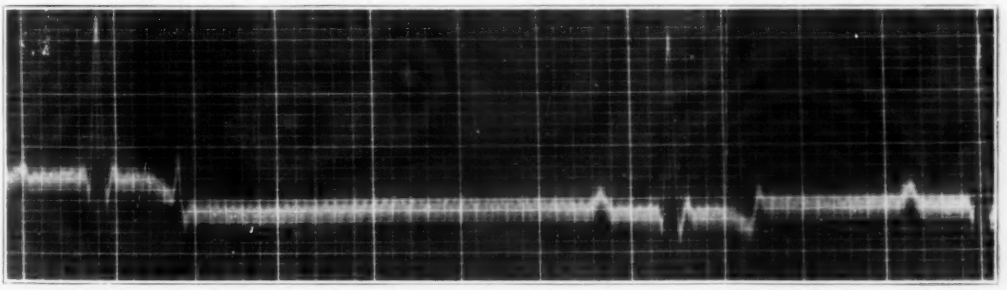

Fig. 3 (dog 5).—Occasional cycle of sino-auricular block four days after the introduction of 0.99 millicurie of radon over the sino-auricular node.

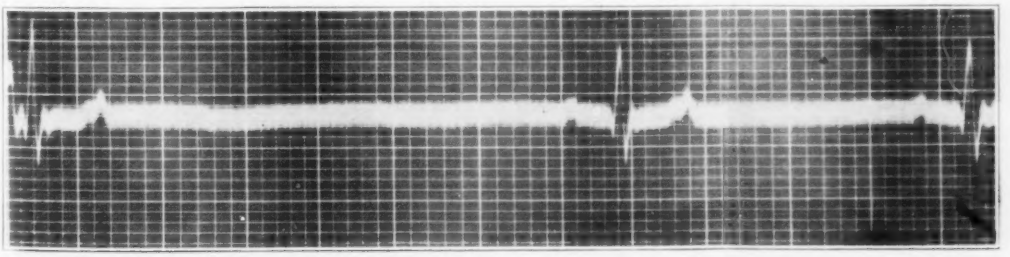

Fig. 4 (dog 6).—Occasional cycle of sino-auricular block ten days after constant exposure of the sino-auricular node to 0.99 millicurie of radon.

In Dog 6 (series of 1927-1928), no noteworthy electrocardiographic changes were observed. Histologically, no nodal tissue was found, and the site of the initiation of impulse was found to be at the coronary sinus. In this experiment there was definite evidence of coronary sinus rhythm with a p-r interval of from 0.12 to 0.14 second and a heart rate of 70, compared with a normal preoperative p-r interval of 0.12 second and a cardiac rate of 80. Under the conditions of this experiment, although two and one-half days after operation there was a shortening of the p-r interval by 0.02 second at the time the method of determining initial negativity was used, 120 days later, the p-r interval was again normal.

In dog 8 (series 1927-1928), on the thirty-eighth day after operation, the cardiac rate and p-r intervals were relatively unchanged, the pulse was found to arise in the region of the coronary sinus, and histologically there was no sino-auricular tissue. Cycles of sino-auricular block were observed during the second week after operation.

In dog 5 (series 1928-1929), in which 4 millicuries of radon was used, more marked changes of rhythm were found. One week after operation, delayed conduction and as many as seven consecutive cycles of nodal rhythm at the rate of 37.5 per minute interspersed between normal cycles and occasional right ventricular premature beats were found. In this animal no sino-auricular tissue was found histologically, and the impulse was found to arise from the coronary sinus. The normal preoperative p-r interval was from 0.13 to 0.14 second and the cardiac rate 90, and thirty-seven days after operation, in the presence of what seemed electrocardiographically to be a normal rhythm, the p-r interval was from 0.11 to 0.12 second and the cardiac rate only 39. This bradycardia seems significant in that it further suggests the initiation of the impulse in the coronary sinus.

In dog 9 (series 1928-1929), after operation, a series of cycles of nodal rhythm was noted together with evidence of decreased cardiac vagal tone. Before operation the p-r interval was from 0.12 to 0.15 second, and after operation it had increased until it was from 0.14 to 0.17 second. Before and after operation there was an inverted T^2 wave, and during the introduction of the tube of radon this animal was the only one in which an auricular fibrillation was produced. Terminally, the coronary sinus was found initially negative, and histologically no nodal tissue was found.

In dog 13 (series 1928-1929), the sino-auricular node was initially negative, and histologically the crista terminalis showed a visible nutrient artery with extensive coagulation necrosis and hemorrhage into the surrounding tissue. It was inconceivable that such tissue could function. In this animal occasional cycles of sino-auricular block were observed, but no other electrocardiographic changes were noted.

In dog 19 (series 1928-1929), histologically, there was a similar destruction of tissue at the site of the sino-auricular node, while the impulse originated terminally in the sino-auricular nodal area. On the twelfth day after the introduction of radon, the animal was in almost

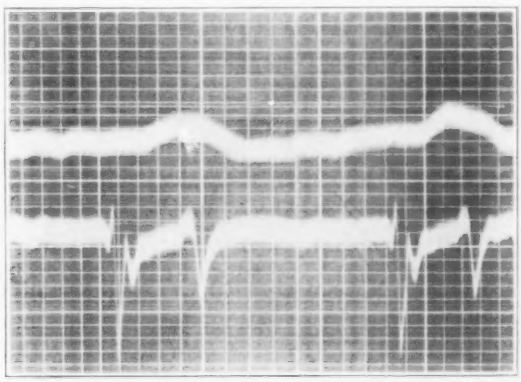

Fig. 5.—The right electrode on the sino-auricular node; the left, on the body of the right auricle. Result: auricle initially negative. (Figures 5, 6, 7 and 8 represent experiments on initial negativity in dog 6; in each record the upper wave indicates auricular contractions, the lower wave, simultaneous direct electrocardiograms.)

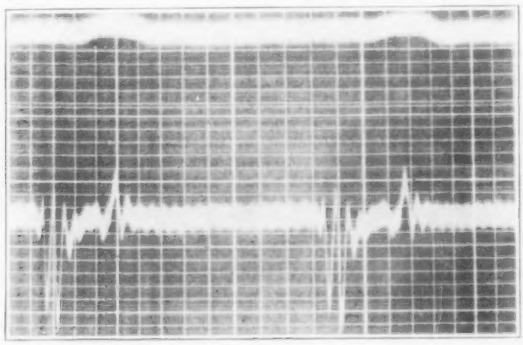

Fig. 6.—The right electrode was on the sino-auricular node; the left, on the coronary sinus. Result: coronary sinus initially negative.

complete nodal rhythm. At the end of the experiment, prior to the determination of the initial negativity, only an occasional nodal cycle was observed, and the p-r interval had been reduced to from 0.09 to 0.11 second from a normal preoperative p-r interval of from 0.135 to 0.165 second.

In three of the seven animals the sino-auricular node proved to be initially negative, but the gross and histologic changes in this region were so extensive as to render it unlikely that the sino-auricular node could function. For this we offer no certain explanation. It is barely possible that the immediate surrounding tissue initiated the cardiac impulse or that small outlying remnants of the sino-auricular node escaped destruction and initiated the impulse. In each of the seven experiments the point of initial negativity remained unchanged throughout that single experiment when compared with all outlying points. If the electrodes were changed, the observations were the same. Therefore, we place greater reliance on the observations of initial negativity than on the negative histologic observations.

In no experiment have we been able to obtain a permanent auriculoventricular nodal rhythm. This corroborates the observations of others and ourselves. We attribute the shorter period of nodal rhythm in our experiments as compared with other experiments in which the sino-auricular node had been ligated and excised to the more gradual process of destruction in the experiments with radon. This fact indicates the greater reliability of the method using radon, and also verifies previous observations in the more acute experiments.

The finding of cycles of auriculoventricular block in these experiments suggests that although the impulses continued to arise from the sino-auricular node directly beneath the implant of radon, changes were brought about that interfered with the transmission of the impulse through the auriculoventricular node. More frequently, however, cycles of sino-auricular block were noted which suggested that there was interference with the impulse originating in the sino-auricular node during its transmission to the auriculoventricular node.

In several instances it was observed that following the hypodermic administration of ½ grain (0.0324 Gm.) of morphine sulphate, nodal rhythm followed in animals showing postoperative changes in rhythm such as sino-auricular block and cycles of nodal rhythm. This suggests that the early stimulating vagal effect of morphine is more effective in inhibiting the functioning of the coronary sinus than that of the normal sino-auricular node. Therefore, in the normal dog, it is possible that if the administration of morphine produces a nodal rhythm it might be inferred that the animal had a coronary sinus rhythm prior to the injection of the drug, or that the vagal tone was excessively great. This point, however, needs further verification.

No matter what the actual process underlying the electrocardiogram may prove to be, whether it is produced by the passage of the impulse along specialized tissue or whether it is due to chemical changes or to actual muscular contraction, there can be no doubt that the shape and time relation of the waves secured by the usual leads depends on the

order in which the excitation sweeps over the heart. The real problem in our experiments is to account for the normal electrocardiograms when the sino-auricular node is destroyed, when the pacemaker must be in a lower part of the specialized tissue and when excitation must be

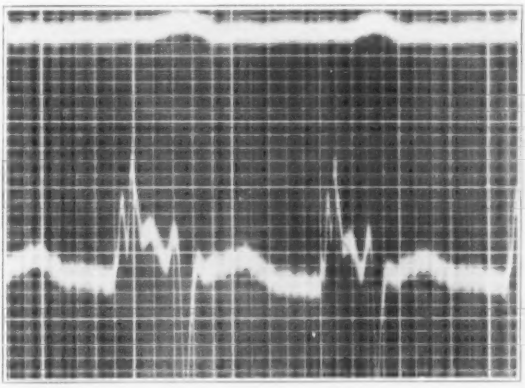

Fig. 7.—The right electrode was on the coronary sinus; the left, on the body of the right auricle. Result: coronary sinus initially negative.

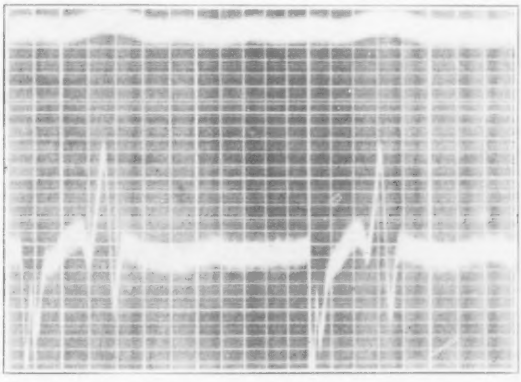

Fig. 8.—The right electrode was on the auriculoventricular node; the left, on the coronary sinus. Result: coronary sinus initially negative.

delivered to the myocardium at other than the usual place. If excitation were instantaneously transmitted, as Mackenzie [3] believed, there might

3. Mackenzie, James: Diseases of the Heart, London, H. Frowde, Hodder & Stoughton, 1923, p. 424.

be a way out of our difficulties, but this idea is not tenable in the light of present information. The question is: How can the coronary sinus, the undoubted seat of initial negativity in some of our experiments, deliver a stimulus to the auricle so that the p wave is normal in all of its characteristics and the p-r interval of the usual value? At present, we have no answer to the question that is based on experimental evidence. It may be that the impulse from the coronary sinus reached the auricle over a pathway to the region of the sinus and thus was finally distributed in the usual manner. Although it is difficult to understand how this could take place in view of the extensive and advanced destruction of the sino-auricular nodal tissue, it is more difficult to see that there should be no reduction in the p-r interval.

Eight years ago, Eyster and one of us [1] noted a decrease in the p-r interval of 0.03 second and about a 25 per cent decrease in the average cardiac rate in coronary sinus rhythm in dogs in which the sino-auricular nodes had been ligated and excised. It is possible that

TABLE 3.—*Data of a Previous Series of Fourteen Dogs*

	Preoperative		Days After	Postoperative	
Dog	p-r Interval	Cardiac Rate	Operation	p-r Interval	Cardiac Rate
2	0.09-0.12	100	81	0.08-0.10	70
			185	0.10-0.11	120
7	0.12-0.13	120	14	0.08-0.10	120
			22	0.12-0.13	130
10	0.09-0.10	100	9	0.06-0.08	70
			137	0.09-0.10	110

in the experiments in which destruction is sudden, certain factors obtain which are not present in experiments in which that destruction is slow, as when it is produced by radon. We have no other explanation to offer for the fact that in the experiments reported herein the p-r interval and the cardiac rate remained normal. It is noted that the period of observation after the destruction of the sino-auricular nodes in the present series is over a much longer period of time than in the series reported by Eyster and Meek. In a personal conversation, Dr. Pierre Ryland of Belgium stated that he had noted many examples of coronary sinus rhythm. He expressed the belief that interference with the supply of blood in the sino-auricular region allowed the auriculoventricular node to gain a temporary ascendency over the region of the coronary sinus.

An examination of the data in a previous series of fourteen dogs in which the sino-auricular node was destroyed by radon [2] revealed the results recorded in table 3.

While these animals (dogs 2, 7 and 10) showed decreased p-r intervals and cardiac rates after operation, after the lapse of a certain

interval of time normal figures for these values were obtained; in some animals normal rates were found for an extended period. In dog 2, on the eighty-first day after operation there was still evidence of what might be interpreted as coronary sinus rhythm. In these three animals careful histologic examination revealed the absence of sino-auricular tissue and the replacement thereof with scar tissue and extensive degenerative changes. This observation suggests that possibly if the animals concerning which Eyster and one of us (W. J. M.) reported had been observed over a longer period, a return to normal figures might have occurred.

CONCLUSIONS

1. The previous observation that the nodal tissue of the coronary sinus apparently acts as a reserve mechanism, as a pacemaker under conditions of experimental destruction of the sino-auricular node, is corroborated.

2. Evidence is presented that suggests that a coronary sinus rhythm cannot be differentiated from a sino-auricular rhythm by means of an electrocardiogram.

3. If the sino-auricular node is destroyed gradually by radon, the nodal tissue of the coronary sinus assumes the function of pacemaker.

4. It is probable that when the sino-auricular node is rendered functionless by disease the nodal tissue of the coronary sinus acts as pacemaker.

5. Permanent nodal rhythm, i. e., a rhythm with a definite and permanently shortened p-r interval, cannot be produced by destroying the sino-auricular node with radon.

6. Nodal rhythm temporarily follows the injection of morphine in dogs in which the sino-auricular nodes have been destroyed by radon.

7. The electrocardiographic changes in dogs following the destruction of the sino-auricular nodes by radon are: temporary reduction of the p-r interval, which later becomes normal, slightly greater or slightly less than normal; decreased cardiac vagal tone; partial and complete sino-auricular block; partial and complete auriculoventricular block; nodal rhythm; coronary sinus rhythm; inverted T^2 and T^3, and premature ventricular beats.

THE APPEARANCE OF HISTIOCYTES IN THE PERIPHERAL BLOOD*

WILLIAM DAMESHEK, M.D.
BOSTON

REVIEW OF THE LITERATURE

Although the histiocyte is occasionally seen in the peripheral blood, it is usually unrecognized, chiefly, it seems, because the existence of the cell in the circulation is not generally known. Therefore, it was felt that a review of the subject of the histiocyte and of its appearance in various clinical conditions might arouse more general interest in the appearance of the cell and its clinical significance.

The name "histiocyte" signifies literally "tissue cell." It was first used in this connection by Aschoff [1] and Kiyono in 1913, and has come into use as the generic name for the cells of the reticulo-endothelial system. The word histiocyte has many synonyms: It is the macrophage of Metchnikoff [2] and of Evans,[3] the clasmatocyte of Ranvier [4] and of Sabin and Doan,[5] the adventitial cell of Marchand,[6] the pyrrole-blue cell of Goldmann,[7] the hemohistioblast of Ferrata,[8] the Ferrata cell of various Italian hematologists,[9] the monoblast of Merklen and Wolf,[10]

* Submitted for publication, Oct. 10, 1930.

* From the Medical Service and Department of Pathology, Beth Israel Hospital.

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10. Merklen, M., and Wolf, M.: Leucémies à monocytes, Rev. de méd. **45**:154, 1928.

the "Stammzell" of certain German authors [11] and the resting-wandering cell of Maximow.[12] The last author, writing in 1927,[13] said that although the word histiocyte was more or less meaningless, at least it had world wide acceptance, and therefore its use was probably preferable to that of his own term "resting-wandering cell."

The histiocyte, a large cell containing phagocytosed material, was first described as occurring in the peripheral blood by Eichhorst [14] in 1874. This author described fairly numerous cells from four to six times the size of red blood cells in a case of typhoid fever: they contained from two to seven inclusions of red blood cells. The formation of pseudopods was noted in several cells, a few of which contained vacuoles. Eichhorst thought that these cells were probably derived from the spleen, although he considered derivation from a coincident phlebitis possible. Eichhorst cited Remak (1845), who discovered large cells with inclusions of red cells occurring in the splenic pulp of calves, horses and dogs after venesection, and Gullivier (1842), who found from one to six red blood cells in certain "lymphocytes" in a horse dying of phlebitis. In 1907, Rowley [15] found the phagocytic "lymphocyte" in the blood from patients with tertian malaria and lymphatic leukemia, and in 1908 she described [16] a case of "fatal anemia associated with enormous numbers of circulating phagocytes." The blood from this patient was studied in a warm chamber as well as with fixed preparations. Appended to this article are a large number of excellent photomicrographs showing the process of phagocytosis.[17] In 1907, Van Nuys [18] and in 1911, Leede [19] first found phagocytic cells in subacute

11. Ewald, Frehse and Hennig: Akute Monozyten—und Stammzellen—Leukämien, Deutsches Arch. f. klin. Med. **138**:353 (Feb.) 1922.

12. Maximow, A.: Untersuchungen über Blut und Bindegewebe, Arch. f. mikr. Anat. **73**:444, 1909.

13. Maximow, A.: Les rélations des cellules sanguines avec le tissu conjonctif et avec l'endothelium, Ann. d'anat. path. **4**:701, 1927.

14. Eichhorst, H.: Ein merkwürdiger Fund im Blute eine Typhuskranken, Deutsches Arch. f. klin. Med. **14**:223, 1874.

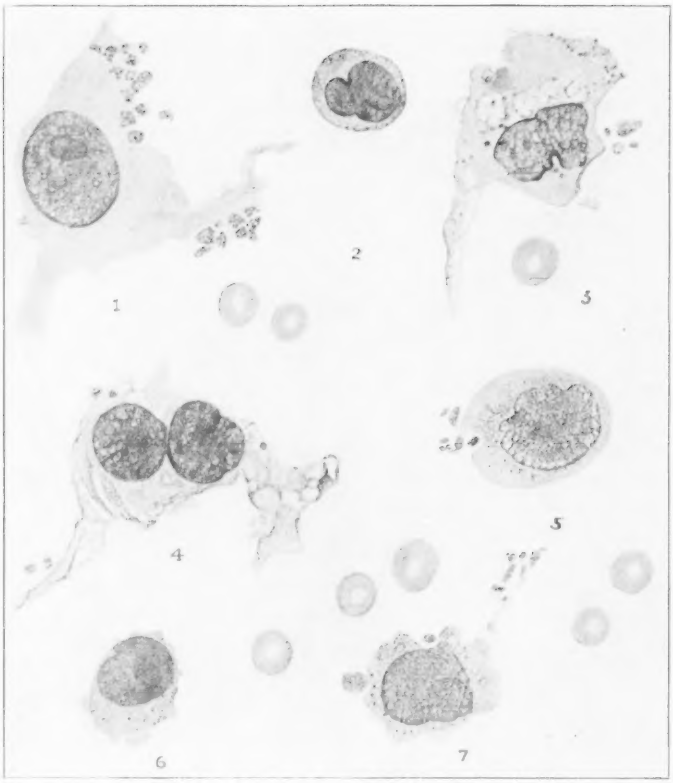
15. Rowley, M. W.: The Occurrence of Atypical Phagocytic Cells in the Circulating Blood, New York State J. Med. **85**:674, 1907.

16. Rowley, M. W.: A Fatal Anemia with Enormous Numbers of Circulating Phagocytes, J. Exper. Med. **10**:78, 1908.

17. The rapidly developing anemia and the extremely high leukocyte count (800,000 per cubic millimeter before death) strongly indicate the diagnosis of monocytic leukemia. This would antedate by five years Reschad and Schilling's observation of the first reported case (Ueber eine neue Leukämie durch echte Uebergangsformen [splenozytenleukämie], München. med. Wchnschr. **60**:198, 1913).

18. Van Nuys, F.: An Extraordinary Blood: Presence of Atypical Phagocytic Cells, Boston M. & S. J. **156**:390, 1907.

19. Leede, W.: Ein Fall von Endocarditis ulcerosa mit krankhaftentartenden Lymphozyten im Blut, Mitt. a. d. Hamb. Staatskrankenanst. **12**:411, 1911.



Cells from preparations stained according to Wright's method; reduced from × 1,200. Nos. *1*, *2* and *3* are from a case of dementia paralytica in which frequent convulsions occurred; *5*, *6* and *7*, from a case of monocytic (histiocytic) leukemia. No. *1*, an extremely large histiocyte. Several platelets seem to have become phagocytosed; the nucleolus in the spongy nucleus is prominent. No. *2*, an ordinary monocyte. The fine granules in the grayish-blue cytoplasm and the fine chromatin network of the indented nucleus are to be noted. No. *3*, a histiocyte with a large amount of ingested débris. Vacuole formation is common in these cells. No. *4*, the possible beginning of a giant cell. This has occurred in a histiocyte that has probably undergone amitotic division of the nucleus. Note the phagocytosed platelets and the vacuoles. The bizarre shapes of the cells *1*, *3* and *4* are due to their marked motility and pseudopod formation, although cell *4* has probably become somewhat broken. No. *5*, the perfect histiocyte. Note the spongy character of the nuclear chromatin and the perinuclear arrangement of the granules. No. *6*, a cell apparently a transition between the typical histiocyte of *5* and *7* and the typical monocyte of *2*. There are more pseudopod formation, a rounder nucleus and coarser granules than in the ordinary monocyte. No. *7*, another typical histiocyte seen in a more "active" stage than the cell *5*. Nos. *5*, *6* and *7* were seen in one oil-immersion field in a case of monocytic leukemia.

bacterial endocarditis. This observation has been repeated by so many observers that the phagocytic histiocyte seems to have become identified with that disease. In 1912, Connal [20] found phagocytic cells in trypanosomiasis, malaria, smallpox and ankylostomiasis; he felt that the cells appeared while immunity was being acquired. Neukirch [21] found cells containing pigment bile in a case of jaundice, and Kraus [22] found phagocytic cells in a case of splenomegaly. Netousek [23] discovered these cells in cases of subacute bacterial endocarditis, typhoid fever and cholera and occasionally in other conditions; he also found suspected "Endothelien" at times in normal blood. In 1918 and 1919, Kaznelson [24] wrote the first general article on this subject and described the finding of histiocytes in a case of streptococcic pyemia and in one of general tuberculosis of the lymph nodes; in both of these cases hemorrhagic diathesis was present.

Kaznelson cited the finding of histiocytes by various authors in paroxysmal hemoglobinuria and in pernicious anemia. The first adequate descriptions of the cells are given by Ferrata and his associates.[25] Ferrata called these cells "hemohistioblasts" and expressed the belief that they are the forerunners of all the blood cells. He and his associates pointed out the occurrence of these cells in the leukemias, especially in monocytic leukemia. Complete descriptions of the cell and of its spongy nucleus are given in these articles, which are excellently illustrated with colored plates. The first general article in the American literature is that by Simpson,[26] who studied the histiocytes exhaustively, mainly from the experimental standpoint. She was the first to study the cell systematically by the supravital technic. The subject is touched on by Naegeli [27] in his textbook and is discussed at greater length by

20. Connal, A.: Auto-Erythrophagocytosis in Protozoal Diseases, J. Path. & Bact. **16**:502, 1911.

21. Neukirch, P.: Ikterische Zellen im Blute bei Icterus neonatorum, Ztschr. f. klin. Med. **74**:380, 1911.

22. Kraus, F.: Ein Fall von Splenomegalie, Berl. klin. Wchnschr. **50**:1421, 1913.

23. Netousek, M.: Ueber Endothelien und ihre Beziehung zu den Monozyten, Folia haemat. **19**:1, 1914.

24. Kaznelson, P.: Seltene Zellformen des strömenden Blutes (Megakaryocyten, Histiocyten, Endothelien), Deutsches Arch. f. klin. Med. **128**:131, 1918.

25. Franco and Ferrata (footnote 8). Reitano (footnote 9). Esposito, A.: Morfologia e significato anatomico degli emoistioblasti nelle leucemia, Haematologica **4**:269, 1923. Ferrata, A., and Negreiros-Rinaldi: Emoistioblasti e monociti nella milza malarica, Haematologica **1**:243, 1920.

26. Simpson, M. H.: The Experimental Production of Macrophages in the Circulating Blood, J. M. Research **53**:77, 1922.

27. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 4, Berlin, Julius Springer, 1923.

Schilling,[28] who was responsible for some of the earlier observations on the histiocyte, especially in malaria. Schittenhelm[29] gave a general review. Sabin and Doan[5] studied the "clasmatocytes" with their supravital technic. Other papers of general interest are those by Richter[30] and Vasiliu.[31]

MORPHOLOGY OF THE HISTIOCYTE

The most extensive work on the morphology of the histiocyte in fixed sections of tissue has been done by Maximow.[32] Ordinarily two types of histiocytes are recognized: the reticular cell and the "endothelial" cell. These cells are large and contain large vesicular nuclei. The reticular cell differs from the endothelial cell in that it is situated in the stroma of various organs; its cytoplasm has long fibrillary processes that apparently bind together other cellular structures. These cells are characteristically seen in the spleen, bone marrow and lymph nodes. The endothelial cells line very small blood vessels or sinusoids in the liver, bone marrow, lymph nodes and spleen. There has been some discussion concerning whether or not these cells are identical with the reticular cells; Maximow[33] expressed the belief that the grouping of endothelial cells about tiny blood vessels was more apparent than real. Together these two types of cells make up the reticulo-endothelial system.

Because the various processes involved in the fixation and staining of sections of tissue distort the cells to some extent, the morphology of the histiocyte is studied best in blood smears. In these preparations it is seen that the histiocyte is by far the largest of the circulating cells, measuring from 15 to 40 microns in diameter. Its shape is extremely variable, chiefly because of its marked powers of locomotion. It is usually oval; frequently it is round or polygonal, but it may be long and kite-shaped.[34] The cytoplasmic membrane is indefinite and usually shows budding or pseudopods, which often gives the cell a bizarre

28. Schilling, V.: The Blood Picture and Its Clinical Significance, English edition, St. Louis, C. V. Mosby Company, 1929.

29. Schittenhelm, A.: Normale und pathologische Physiologie des retikuloendothelialen Systems, Handbuch der Krankheiten des Blutes under der blutbildenden Organe, Berlin, Julius Springer, 1925, vol. 2, p. 492.

30. Richter, M. N.: Observations on the Hemohistioblast of Ferrata, Am. J. M. Sc. **169**:336, 1925.

31. Vasiliu, T.: Sur la présence des cellules primitives migratrices dans le sang circulant, Mém. de la Soc. de biol. **88**:934, 1923.

32. Maximow, A.: The Macrophages or Histiocytes, in Cowdry, Edmund V.: Special Cytology, New York, Paul B. Hoeber, Inc., 1928, vol. 1, chap. 14.

33. Maximow (footnotes 13 and 32).

34. On the basis of variations in size and shape, Sabin and Doan (footnote 5) divided these cells into four types: long, small round, large round and very large.

appearance. In color, the cell is weakly basophilic; it stains sky blue with Wright's stain, and it often has a "ground-glass" appearance. The granules, which are usually azure, are occasionally bluish; they are coarser than those in the monocyte. They are characteristically grouped about the nucleus, and are rarely found at the periphery of the cell.[35] There is often vacuolization of the cytoplasm, and phagocytosed particles are seen at times. The latter may be composed of fragments of cells or even of entire red blood cells, white blood cells or platelets, as well as of bacteria or particles of pigment. When any of these particles are present, vacuoles are commonly seen. The nucleus is round or egg-shaped; usually it is centrally placed and is about one-half the size of the cell. Sometimes the nucleus is slightly indented, in which case the cell resembles more closely the ordinary monocyte. The nuclear membrane is distinct and heavy, and the nuclear chromatin is spongy in appearance, as Ferrata first pointed out. This spongy appearance is distinctive and, together with the other criteria, previously outlined, usually makes recognition of the cell easy.

At times, on account of the marked fragility of the cell, it appears to be broken up or to consist almost entirely of a nucleus with a faint and indefinite border of cytoplasm. In these cases, as Sabin and Doan[2] have pointed out, the definite nuclear membranes and the indefinite cytoplasm are usually enough to make the diagnosis of the cell possible.

Preparations supravitally stained by the method of Sabin[36] serve to emphasize interesting functional characteristics of the cell. It moves rapidly at a temperature of 37.5 C., so that there is continual shifting of the cytoplasm. Pseudopods constantly protrude, changing the cellular shape from oval to elongated and back again within a minute or two. Some of the shapes assumed are bizarre and account for the marked variation in appearance of the cell in stained preparations. At times, the cell is seen to surround a red blood cell or a group of blood platelets, which are then incorporated in its cytoplasm. When this occurs, the movements of the cell become extremely rapid; after a minute or two, vacuoles appear in the cytoplasm. As Kiyono[37] and Patella[38] pointed out, amitotic division of the cell rarely takes place, the cell divid-

35. Some authors, notably Ferrata and members of his school (footnotes 8 and 25) laid great emphasis on the color of the granules. Chiefly on the basis of these differences, they claimed to separate the histiocytes into various types—myeloid, lymphoid and monocytoid. These distinctions have not been made out in the present work. In fact, histiocytes from the same case may show marked differences in the staining characteristics of the granules.

36. Sabin, F. R.: Studies of Living Human Blood Cells, Bull. Johns Hopkins Hosp. **34**:277, 1923.

37. Kiyono, K.: Die vitale Carminspeicherung, Jena, Gustav Fischer, 1914.

38. Patella, V.: La genesi endoteliale dei monociti, delle forme di passagio e dei cosidetti linfociti del sangue, Haematologica **4**:59, 1923.

ing into two parts which continue to move about as separate cells. There is a sprinkling of neutral red granules throughout the cell; these do not shift into the newly formed pseudopod unless the latter remains stationary for more than a few seconds. This lack of shifting of the granules into the periphery of the cell accounts for the characteristic central arrangement of the granules in the stained preparations. The mitochondria, which are brought out by the use of janus green, are seen as delicate filaments interspersed throughout the cytoplasm. The nucleus changes its shape readily with change in shape of the remainder of the cell. Grouping of the neutral red granules at the centrosphere may occur, but there is no characteristic grouping in the "Hof" of the nucleus as in the ordinary monocyte. In cases showing marked monocytosis and histiocytosis, cells may be seen that are apparently intermediate between the typical histiocyte and the typical monocyte. Accurate differentiation between the two then becomes impossible.

Staining of the histiocyte with oxidase by the method of Sato and Yoshimatsu[39] has given negative results in this work, although some authors found positive granules in certain cells. Doan and Sabin[40] said that the cells give positive results when stained with oxidase only if they contain ingested material that gives a positive reaction on staining. They suggested that the method used has probably a great deal of significance in the evaluation of results.

Cultures of the histiocytes have been made by Maximow,[41] Avrorow and Timofejevski,[42] the Lewises,[43] Bloom[44] and Carrel and Ebeling.[45]

39. Sato, A., and Yoshimatsu, S.: Peroxidase Reaction in Epidemic Encephalitis: A New Diagnostic and Prognostic Method, Am. J. Dis. Child. **29**:301 (March) 1925.

40. Doan, C. A., and Sabin, F. R.: Normal and Pathological Fragments of Red Blood Cells: Phagocytosis of These Fragments by Desquamated Endothelial Cells of the Blood Stream: The Correlation of the Peroxidase Reaction with Phagocytosis in Mononuclear Cells, J. Exper. Med. **43**:839, 1926.

41. Maximow, A.: Ueber die Entwicklungsfähigkeiten der Blutleukocyten und des Blutgefässendothels bei Entzündung und im Gewebskulturen, Klin. Wchnschr. **4**:1486, 1925.

42. Avrorow, P. P., and Timofejevski, A. D.: Kultivierungsversuche von leukämischen Blute, Virchows Arch. f. path. Anat. **216**:184, 1914.

43. Lewis, M. R.: The Formation of Macrophages, Epithelioid Cells and Giant Cells from Leukocytes in Incubated Blood, Am. J. Path. **1**:91, 1925. Lewis, M. R., and Lewis, W. H.: The Transformation of White Blood Cells into Clasmatocytes (Macrophages), Epithelioid Cells and Giant Cells, J. A. M. A. **84**:798 (March 14) 1925.

44. Bloom, W.: Transformation of Lymphocytes of Thoracic Duct into Polyblasts (Macrophages) in Tissue Culture, Proc. Soc. Exper. Biol. & Med. **24**:567, 1927.

45. Carrel, A., and Ebeling, A. H.: The Fundamental Properties of the Fibroblast and the Macrophage: II. The Macrophage, J. Exper. Med. **44**:285, 1926.

The technic of Rhoads and Parker [46] was used in a case of monocytic leukemia; there was little variation in the cell, except that it became much larger and more active, and it showed more phagocytosed particles.

The histiocyte must be distinguished chiefly from the ordinary monocyte, the large lymphocyte and the premyelocyte. The differentiating points have been grouped in table 1.

TABLE 1.—*Data on the Histiocyte and Its Differentiation*

	Histiocyte	Monocyte	Large Lymphocyte	Myeloblast	Premyelocyte	Polymorphonuclear
Size (millimicrons)	15-40	10-20	10-15	6-15	10-20	10-15
Shape	Variable	Oval	Elongated oval	Round to oval	Round to oval	Round
Pseudopods	Common	At times	Rare	Little "tags" at times	None	None
Cytoplasm:						
Color	Sky blue	Grayish blue	Sky blue	Ultramarine blue	Blue, verging to pink	Pink
Granules	Azure; coarse; usually grouped about nucleus	Innumerable; fine; lilac	Large azure in 10 per cent of cells	Absent	Few large blue, red or violet	Many large blue, red or violet
Vacuoles	Common; phagocytosed material often present	Rare	None	Rare	None	Rare
Nucleus:						
Size	About one-half size of cell	Relatively large	One-half size of cell; eccentric	Fills almost entire cell	Large	Variable
Shape	Round to oval	Usually reniform	Usually round	Oval, rarely indented	Round	Polymorphous
Character of chromatin	Spongy	Fine network	Thick blocklike masses	Extremely fine mesh	Coarse linear	Coarse linear
Nucleoli	Rare	Absent	Absent	1 to 5 in each cell	Occasional	None
Oxidase reaction	Negative	Fine, sparse positive granules	Negative	Positive	Positive	Positive
Supravital staining	Active ameboid motion	Ameboid motion; arrangement of granules	No motion	No motion	No motion	Granules move, "stream" and push cell

Thus the histiocyte is a definite cell with certain characteristic qualities—structural, tinctorial and physiologic. It is a cell that rarely appears in the blood stream. Its differentiation from other blood cells, particularly from the monocyte, becomes difficult at times. The histiocyte and the monocyte often merge by almost imperceptible transitions. The

46. Rhoads, C. P., and Parker, F., Jr. Observations on Incubated Normal Bloods, Am. J. Path. **4**:271 (May) 1928.

histiocyte is thought by many to be the forerunner of the monocyte, and the collection of histiocytes throughout the body is called the reticulo-endothelial system.

THE ORIGIN OF THE HISTIOCYTE IN THE BLOOD

There is still some difference of opinion as to the origin of the histiocyte in the peripheral blood, though the concensus is that it is a free cell of the reticulo-endothelial system. Sabin and Doan [5] have maintained that the histiocyte is a fourth type of blood cell (the other types being the granulocyte, the lymphocyte and the monocyte); they have thus sharply separated the histiocyte from the monocyte. They expressed the belief that the monocyte is derived directly from the mesenchymal reticular cells, whereas the clasmatocyte is derived from the desquamation of endothelial cells that line the sinusoids in the liver, the bone marrow and the spleen or are present in diffuse connective tissue. Sabin and Doan [5] observed, chiefly in embryologic studies, the direct dropping off of endothelial cells into the lumina of blood vessels with the subsequent appearance of histiocytes. They separate histiocytes from monocytes largely on the basis of their morphology as seen in supravital preparations, and they maintain that the histiocytes are present in blood from normal human beings (up to 4 per cent) in 80 per cent of blood counts. They felt that the constant desquamation of endothelial cells into the circulation is responsible for the appearance of the phagocytic cells, which are often seen as smudges or even as free nuclei in fixed preparations. On the other hand, the following objections may be raised to their conceptions: (1) lack of proof that the monocyte and the histiocyte are derived from separate sources; (2) the underemphasis of the fact that histiocytes appear in increased numbers in conditions in which monocytosis is present; (3) the lack of mention of cells that are apparently transitions between histiocytes and monocytes, and (4) the minimizing of the vast amount of work that has been done on the reticulo-endothelial system and that has shown chiefly that the "reticular" cell and the "endothelial" cell react in much the same way to dyes and other materials, and that they probably are variations of the same cell.

Since his original work in 1898, Mallory [47] has felt that new histiocytes (or endothelial leukocytes) are derived directly, even in the adult, from the endothelium lining ordinary blood vessels. This view has been strongly called into question by the work of Maximow,[13] Evans [8] and Aschoff,[48] and apparently it is not entirely accepted by Sabin and

47. Mallory, F. B.: A Histological Study of Typhoid Fever, J. M. Research **3**:611, 1898; Principles of Pathological Histology, Philadelphia, W. B. Saunders Company, 1923.

48. Aschoff, L.: Morphologie des retikulo-endothelialen System, in Schittenhelm, A.: Handbuch der Krankheiten des Blutes und der blutbildenden Organe, Berlin, Julius Springer, 1925, vol. 2, p. 473.

Doan.[5] Maximow[32] said definitely that the histiocytes of the blood were simply free cells of the reticulo-endothelial system.

Ferrata[25] expressed the belief that the hemohistioblast—a primitive blood cell derived directly from the embryonic mesenchyme—is potentially the precursor of all blood cells, and that three types of circulating hemohistioblasts—myeloid, lymphoid and monocytoid—are distinguishable chiefly on the basis of difference in granules. It seems rather dubious that the granular hemohistioblast should lose its granules to form the nongranular myeloblast which later again takes on granules to form the myelocyte.

On the basis of an extensive experience in the culture of normal blood from numerous species of animals, the Lewises[43] concluded that histiocytes are more probably derived from monocytes than vice versa. They, as well as Carrel and Ebeling,[45] expressed the belief that monocytes and histiocytes are different phases of the same type of cell.

However, the following views generally accepted at present are that: The histiocyte is the generic name for the cells comprising the reticulo-endothelial system. Although the histiocyte may be potentially a precursor of all blood cells, it is usually incapable of much differentiation in adult life, except that it becomes a monocyte by direct transition or mitosis.[49] The histiocyte has the same relationship to the monocyte that the myelocyte has to the mature polymorphonuclear cell. There are not four types of blood cells, as Sabin and Doan maintained, but three.

A vast literature has accumulated on the subject of the reticulo-endothelial system, especially in the last few years. This literature has been adequately reviewed by Aschoff,[48] Schittenhelm,[29] Maximow,[32] Krumbhaar,[50] Bloom[51] and others. A widely scattered group of cells was incorporated into a "system" by Aschoff[1] and Kiyono after work

49. Schilling, V.: Ueber hochgradige Monocytosen mit Makrophagen bei Endocarditis ulcerosa und über die Herkunft der grossen Mononukleären, Ztschr. f. klin. Med. **88**:377, 1919. Weicksel, J.: Ueber die grossen Mononukleären und Uebergangsformen Ehrlichs (Monocyten) und ihr Verhalten bei Tuberkulose, Med. Klin. **16**:1326, 1920. Weill, P.: Ueber Erythrophagocytose im strömenden Blute, Folia haemat. **26**:27, 1920. Schittenhelm, A., and Erhardt, W.: Untersuchungen über die Beziehungen des reticulo-endothelialen System zu den grossen Monocyten des Blutes mit Hilfe der Vitalspeicherung, Ztschr. f. d. ges. exper. Med. **46**:225, 1925. Paschkis, K.: Zur Frage der Abstammung der grossen Mononucleären, Virchows Arch. f. path. Anat. **259**:316, 1926. Masugi, M.: Ueber die Beziehungen zwischen Monozyten und Histiozyten, Beitr. z. path. Anat. u. z. allg. Path. **76**:396, 1927.

50. Krumbhaar, E. B.: The So-Called Reticulo-Endothelial System, Internat. Clin. **2**:280, 1925.

51. Bloom, W.: The Origin and Nature of the Monocyte, Folia haemat. **37**:1 (Oct.) 1928.

with vital dyes by Ribbert,[52] Goldmann[7] and Tschachin[53] had shown the functional identity of these cells. Maximow[41] studied intensively their embryologic and cultural qualities. Other investigations disclosed their importance in the abnormal storage of fat as in the lipoidemia of diabetes mellitus,[54] in lipoid histiocytosis,[55] in Gaucher's disease[56] and in xanthomatosis.[57] These cells were found to be concerned in the formation of bile from hemoglobin,[58] in the production of immunity against disease[2] and in the phagocytosis of bacterial organisms.[47] Reticuloendotheliosis[59]—leukemic and aleukemic—has recently been described; the leukemic form is generally known as monocytic (histiocytic) leukemia.[60]

THE APPEARANCE OF HISTIOCYTES IN THE PERIPHERAL BLOOD

From the standpoint of pathologic physiology, it seems logical to search for histiocytes in the peripheral blood in any condition in which irritation of the reticulo-endothelial system—irrespective of its cause—is known to occur. Although Sabin and Doan[3] found these cells in 80 per cent of normal subjects, they have not otherwise been described in normal conditions except by Uyeyonahara,[61] who used a special supravital technic, and possibly by Netousek.[23] In an examination of at least 10,000 blood smears in the past three years, histiocytes have not been found in normal persons. Their appearance was limited to the abnormal conditions described in the following paragraphs.

Monocytic Leukemia.—Two cases of this rare disease were observed.[55] This disease was characterized by an acute course with the

52. Ribbert, H.: Die Abscheidung intravenös injezierten gelösten Karmins in den Geweben, Ztschr. f. allg. Physiol. **4**:201, 1904.

53. Tschachin, S.: Ueber die "ruhenden Wanderzellen" und ihre Beziehungen zu den anderen Zellformen des Bindesgewebes und zu den Lymphozyten, Folia haemat. **17**:318, 1913.

54. Schultze, W. H.: Ueber grosszellige Hyperplasie der Milz bei Lipoidämie (Lipoidzellenhyperplasie), Verhandl. d. deutsch. path. Gesellsch. **15**:47, 1912.

55. Bloom, W.: Splenomegaly (Type Gaucher) and Lipoidhistiocytosis (Type Niemann), Am. J. Path. **1**:595, 1925.

56. Epstein, E.: Beitrag zur Pathologie der Gaucherschen Krankheit, Virchows Arch. f. path. Anat. **252**:157, 1924.

57. Rowland, R. S.: Xanthomatosis and the Reticulo-Endothelial System, Arch. Int. Med. **42**:611 (Nov.) 1928.

58. Haldeman, K. O.: A Histologic Study of the Formation of Bile Pigment, Arch. Path. **7**:993 (June) 1929.

59. Sachs, F., and Wohwill, F.: Systemerkrankungen des retikuloendothelialen Apparats und Lymphogranulomatose, Virchows Arch. f. path. Anat. **264**: 640, 1927.

60. Dameshek, W.: Acute Monocytic (Histiocytic) Leukemia, Arch. Int. Med. **40**:718 (Oct.) 1930.

61. Uyeyonahara, T.: Studien über menschliche Blut-Histiozyten mittels vitaler Karminspeicherung in vitro, Folia haemat. **40**:1, 1930.

appearance of from 70 to 80 per cent of histiocytes and monocytes. The leukocyte count before death in both cases was 140,000 per cubic millimeter. Studies with supravital staining were done; the histiocytes were extremely active; at times differentiation from the monocytes was very difficult. With Wright's stain, apparent transitions between the typical histiocytes and the typical monocytes could be made out. A postmortem examination was made in neither case, though studies on the bone marrow were carried out in the second case. In the other cases reported an intense proliferation of the reticulo-endothelial system with infiltration of the organs with histiocytes was always seen.

Agranulocytosis.—This condition, in which the granulocytes disappear from the circulating blood, is probably due to direct action by bacteria or their toxins on the leukocytes of the bone marrow. It probably

TABLE 2.—*Agranulocytosis*

Case	Date	White Blood Cells, per C.Mm.	Monocytes, per Cent	Histiocytes, per Cent
3	2/ 7/29	2,500	43.0	2.0
	2/ 8/29	4,650	49.0	6.0
5	5/11/29	880	60.0	5.0
7	12/27/29	8,000	28.0	9.0
	12/29/29	7,600	11.6	1.2
8	3/ 2/30	5,500	43.0	19.0
	3/ 3/30	5,500	33.5	15.0
	3/ 5/30	12,000	30.4	0.8
	3/ 6/30	10,000	10.0	0.0
	3/ 7/30	18,000	17.5	0.5
	3/ 9/30	15,000	12.0	1.0
	3/11/30	15,000	10.0	1.0

represents, not a disease entity, but an atypical reaction to sepsis. Secondary monocytosis has been reported frequently, though histiocytes have not as yet been described. At autopsy, enlargement of the spleen due at least partly to the proliferation of the reticulo-endothelial system has been observed. Nine cases of this disorder have been observed by me,[61a] and in cases 3, 5, 7 and 8, histiocytes were found. In cases 7 and 8, in which recovery took place, there was marked monocytosis and histiocytosis during the phase of recovery. Monocytes and histiocytes numbered 28 per cent of the white blood cells in case 7 and 42 per cent in case 8. As the patient's condition improved, there was a decrease in the monocytic cells. This histiocytic-monocytic phase has recently been reproduced by Fried and me[62] in rabbits suffering from experimental bacterial agranulocytosis.

61a. Dameshek, W., and Ingall, M.: Agranulocytosis (Malignant Neutropenia), Am. J. M. Sc. **181**:502 (April) 1931.

62. Fried, B. M., and Dameshek, W.: Experimental Agranulocytosis, to be published.

Septicemia.—Histiocytes have been observed in cases of generalized sepsis by Kaznelson,[24] Neukirch,[21] Richter [30] and Schittenhelm.[29] In the present study they were found in five cases of septicemia in which the organism was recovered from the blood stream before death. The first three patients died. In an overwhelming infection, the reticulo-endothelial system probably becomes stimulated, and histiocytes may appear in the circulation. In these cases histologic examination of the spleen and bone marrow showed marked hypertrophy, an increase in the number of reticulo-endothelial cells and many phagocytic cells that often contained bacteria.

In case 4, one histiocyte contained an inclusion body, probably a deteriorated red blood cell. The immature polymorphonuclear cells noted were determined by the method of Schilling.[28]

Subacute Bacterial Endocarditis.—As previously mentioned, histiocytes have been reported in cases of subacute bacterial endocarditis by numerous observers, so that the finding of these cells is considered of value in establishing the diagnosis. The view has been prevalent that

TABLE 3.—*Septicemia*

Case	Organism	Polymorphonuclear Leukocytes, per 100 Cc.	Immature Neutrophils, per 100 Cc.	Lymphocytes, per 100 Cc.	Monocytes, per 100 Cc.	Histiocytes, per 100 Cc.
1	Streptococcus hemolyticus...	93.0	57.0	0.0	7	5.0
2	Streptococcus hemolyticus...	93.0	40.0	4.0	3	2.0
3	Streptococcus hemolyticus...	88.0	41.5	3.0	9	3.0
4	Bacillus coli.....	74.8	17.5	13.6	9	3.6
5	Streptococcus viridans.....	71.6	4.0	16.4	12	0.8

these histiocytes are desquamated endothelial cells of capillaries. Therefore, in searching for them the customary advice has been to rub the ear vigorously for some minutes before making the blood smear; this presumably would dislodge some of the enlarged endothelial cells from the capillaries. This concept has been vigorously attacked recently by Schilling [28] (compare also Aschoff [63] on this point), who demonstrated that most of the histiocytes, which are produced in large numbers in this condition, probably become infarcted or destroyed in the pulmonary capillaries, and the remainder are swept out into the general circulation.

In the case of a patient, B. S., examination of the blood showed: Jan. 6, 1930, polymorphonuclear leukocytes, 67.2; immature forms of polymorphonuclears, 8.8; lymphocytes, 27; monocytes, 8, and histiocytes, 0.5; April 11, polymorphonuclear leukocytes, 57.5; immature forms of polymorphonuclears, 3; lymphocytes, 31; monocytes, 9.5; histiocytes, 0.5; eosinophils, 1.5, and basophils, 0.5. In S. C., examination of the blood on April 24, 1930, showed: polymorphonuclear leukocytes, 84; immature forms of polymorphonuclears, 2; lymphocytes, 5; monocytes, 11, and histiocytes, 1.

63. Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924.

Rheumatic Fever and Rheumatic Cardiac Disease.—Monocytosis was observed in about 25 per cent of the cases of acute rheumatic endocarditis studied. Invariably, the monocytosis occurred at the beginning of the convalescent period; it was at this stage that histiocytes were occasionally found.

Tuberculosis.—Although the blood picture has been studied in a fairly large number of cases of pulmonary tuberculosis, and although monocytosis is frequently present, histiocytes have been found in only one case:

In a patient, A. C., examination of the blood revealed: polymorphonuclear leukocytes, 67; immature forms of polymorphonuclears, 28; lymphocytes, 10; monocytes, 21; histiocytes, 5, and eosinophils, 2.

Other Infections.—Monocytosis [64] is commonly seen during convalescence from acute pyogenic infections, this is, in the "monocytic

TABLE 4.—*Rheumatic Fever and Rheumatic Cardiac Disease*

Case	Date	Polymorphonuclear Leukocytes, per 100 Cc.	Immature Cells, per 100 Cc.	Lymphocytes, per 100 Cc.	Monocytes, per 100 Cc.	Histiocytes, per 100 Cc.	Eosinophils, per 100 Cc.	Basophils, per 100 Cc.
E. H.	3/20/29	65.5	4.0	25.0	7.0	3.0	3.0	...
B. K.	9/16/29	62.5	28.5	14.0	21.5	4.0	1.5	0.5
H. N.	12/18/28	63.0	12.0	23.0	11.0	2.0	...	...
G. N.	7/29/29	72.5	11.0	13.0	13.5	0.5	...	...
W. S.	5/14/29	70.0	13.0	11.5	15.0	1.0	...	...
A. A.	6/ 3/30	42.0	12.5	43.5	8.0	1.0	...	...

stage of defense" of Schilling.[28] It was during this period that histiocytes were occasionally discovered. Histiocytes were also found in other infectio in which convalescence was not then taking place and in which monocytosis was not present.

Dementia Paralytica.—In a study of the blood picture in seventy-five cases of dementia paralytica made in the Division of Research at the Boston State Hospital, histiocytes in varying numbers (from 0.4 to 6 per cent) were found in 20 per cent of all cases. This represents the first description of the presence of histiocytes in this disease. There is usually a direct correlation between the appearance of histiocytes and the presence of monocytosis of 12 per cent or over; there was no correlation with the treatment given. In none of the cases studied had malarial treatment been given for at least two years. As a matter of fact, it was often in the cases in which treatment had not been given for

64. Monocytosis is considered present when the monocytes number 12 per cent or more of the total leukocyte count.

several years that histiocytes were commonly seen. Such a situation was observed in one remarkable case:

D. S., a man, aged 36, had acquired syphilis at the age of 20. A year later frequent convulsions developed, and he showed the neurologic and spinal fluid signs of dementia paralytica. Intensive treatment was begun, which was followed by a remission for five years. Convulsions then recurred, and they had continued to the time of writing. At the time of the first examinations (Nov. 4 to 7, 1929), from three to five convulsions occurred every night. The polymorphonuclear cells numbered from 20 to 22 per cent, the lymphocytes from 42 to 48 per cent, the monocytes from 28 to 40 per cent and the histiocytes from 1 to 6 per cent. The latter almost invariably contained phagocytosed material, such as red blood cells, platelets, etc., and were usually markedly vacuolated, of bizarre shape and

TABLE 5.—*Other Infections*

Case	Condition	Polymorphonuclear Leukocytes, per 100 Cc.	Immature Cells, per 100 Cc.	Lymphocytes, per 100 Cc.	Monocytes, per 100 Cc.	Histiocytes per 100 Cc.	Eosinophils, per 100 Cc.	Basophils, per 100 Cc.
G. P.	Subsiding acute infection (? type)	86.0	....	1.5	12.5	1.5	...	...
R. W.	Subsiding perinephric abscess	66.6	12.0	16.0	12.5	0.5	...	...
M. B.	Abscess of liver	84.0	18.4	8.4	7.6	1.6	...	...
B. F.	Infectious monocytosis	37.0	47.0	10.0	32.5	0.5	...	...
R. M.	Subsiding mastoiditis	63.0	13.0	24.0	12.5	0.5	0.5	...
M. S.	Subsiding ulcerative colitis	74.0	38.5	11.5	11.0	0.5	...	...
S. H.	Chronic sinusitis	41.5	....	25.0	33.5	4.0	...	...
J. A.	Subsiding infection (? type)	83.0	28.0	6.5	10.0	0.5	...	0.5
W. R.	Subsiding hepatitis	59.0	....	14.5	26.0	6.0	...	...
W. G.	Subsiding mastoiditis	76.5	14.0	11.0	12.0	0.5	...	...
B. B.	Subsiding acute appendicitis	40.5	1.0	37.5	14.5	0.5	7.5	...

extremely active in supravital spreads. After large doses of phenobarbital had been given, the convulsions gradually ceased, and the differential count of the leukocytes became almost normal, the histiocytes disappearing. With the reappearance of convulsions, the differential count again became abnormal and histiocytes reappeared. Again the convulsions were stopped, and again the differential count became normal. At this point, a severe convulsion was induced by puncture of the carotid artery. Counts made before the convulsion were normal, but those made directly afterward were distinctly abnormal and showed the appearance of several histiocytes. There thus seemed to be a definite relationship between the presence of convulsions and the appearance of phagocytic histiocytes.

Blood smears from twenty-five patients with epilepsy failed to show histiocytes. It is interesting to speculate on the relationship of the convulsions to the appearance of the histiocytes. The possibility of increase in the reticulo-endothelial cells in dementia paralytica with consequent liberation of some of them as free histiocytes at the time of convulsion was considered.

Miscellaneous Conditions.—Histiocytes were found in the miscellaneous conditions shown in table 6.

The occurrence of histiocytes in these conditions, chiefly in those in which the lymph nodes, the spleen or both were involved, may be explained on the basis of the presence of large numbers of reticulo-endothelial cells in the aforementioned situations. Involvement of the spleen or lymph nodes from any cause may result in such marked reticulo-endothelial proliferation that histiocytes appear in the circulation. In the leukemias, histiocytes have been noted chiefly by Ferrata and by others of his school,[25] though they were first described in that condition by Rowley.[16] In the case of trichiniasis previously noted,

TABLE 6.—*Histiocytes in Miscellaneous Conditions*

Patient	Condition	Polymorphonuclear Leukocytes, per 100 C.c.	Immature Cells, per 100 C.c.	Lymphocytes, per 100 C.c.	Monocytes, per 100 C.c.	Histiocytes, per 100 C.c.	Eosinophils, per 100 C.c.	Basophils, per 100 C.c.	Promyelocytes, per 100 C.c.	Myeloblasts, per 100 C.c.
F. S.	Anaphylactic enlargement of the lymph nodes	45.0	7.7	25.3	12.3	2.0	...	...	...	...
E. A.	Lymphoblastoma of mediastinum	70.5	3.0	11.0	17.5	2.0	...	...	...	...
B. S.	Carcinoma of lung	46.0	3.0	29.0	23.5	2.5	...	...	...	...
E.	Carcinoma of lung	45.0	1.0	34.0	21.0	2.5	...	...	...	...
W. S. K.	Hodgkin's disease	61.5	4.0	25.0	13.0	2.0	0.5	...	...	...
N. P.	Hodgkin's disease	67.0	2.5	14.0	10.5	2.5	7.5	...	...	...
B. S.	Chronic hypochromic anemia, iron treatment	52.0	...	27.5	11.5	1.0	...	...	...	...
H. K.	Chronic myelogenous leukemia	86.0	35.2	11.6	2.4	0.4	...	...	0.4	94.8
R. P.	Acute myelogenous leukemia	2.8	...	...	0.2	0.2	...	...	...	...
I. H.	Trichiniasis	41.5	9.5	20.5	8.0	1.0	29.0	1.0	...	...

biopsy of the deltoid and gastrocnemius muscles disclosed large numbers of multinucleated foreign-body giant cells with frequent mitoses of the numerous monocytoid cells.

THE CLINICAL SIGNIFICANCE OF THE APPEARANCE OF HISTIOCYTES IN THE PERIPHERAL CIRCULATION

Histiocytes in the peripheral blood have thus been observed in the following conditions: (1) leukemic proliferation of the reticulo-endothelial system (monocytic leukemia), (2) reactions to various infections, namely, in septicemia, subacute bacterial endocarditis, rheumatic fever, agranulocytosis and dementia paralytica, and (3) miscellaneous conditions, particularly in the leukemias or in associated conditions. Except in the cases of severe septicemia in which the monocytes were relatively reduced, it was found that histiocytes tended to appear whenever monocytosis, generally of marked degree, was present. In these instances, cells that presented morphologic characteristics midway between typical

histiocytes and typical monocytes were commonly seen. This evidence suggests that the histiocyte is the earlier cell in the monocyte series, just as the myelocyte (appearing in a severe pyogenic infection) is the earlier cell in the granulocytic series.

That the appearance of histiocytes in the peripheral blood represents either an overactivity or a disorder of the reticulo-endothelial system has not been entirely proved. Combined hematologic and pathologic investigations, however, in monocytic leukemia [65] and in the various infections, in monocytosis produced experimentally by *Bacterium monocytogenes* [66] or by *Bacillus coli*-like organisms [67] and in studies with vital stains [1] give strong indication that a monocytosis with the presence of histiocytes occurs when there is a proliferation of the reticulo-endothelial tissue.

This concept agrees with the observed clinical signs as previously pointed out. The reticulo-endothelial system apparently acts as a secondary line of defense against bacteria, the first line of defense being the polymorphonuclear cells. This is well brought out in the recovery phase of agranulocytosis, both clinical and experimental, and during convalescence from acute infections. As Metchnikoff [2] first pointed out, the macrophages are probably concerned with the development of immunity. The occurrence of histiocytes in the leukemias and in Hodgkin's disease may be explained on the basis of the close proximity or actual participation of histiocytes in the main cellular reaction, some of the histiocytes being pushed out into the blood stream.

SUMMARY AND CONCLUSIONS

1. The histiocyte has distinctive histologic and functional characteristics that make its presence in the peripheral blood stream easily recognized. In disorders that involve the reticulo-endothelial system, the histiocytes may appear in the peripheral blood usually coincident with an increase in monocytes. This is analogous to reactions of the bone marrow in which myelocytes appear in the peripheral blood coincident with an increase in polymorphonuclear cells.

2. Histiocytes in the peripheral blood were found especially when monocytosis was present. Thus they were seen in monocytic (histiocytic) leukemia, in agranulocytosis, especially in the phase of recovery, in septicemia, in subacute bacterial endocarditis, in the convalescent stage of rheumatic fever and rheumatic endocarditis, rarely in tuber-

65. Schwirtschewskaja, B.: Ueber leukämische Retikuloendotheliose, Virchows Arch. f. path. Anat. **267**:456, 1928.

66. Lang, F. J.: Zur Monozytenfrage, Folia haemat. **36**:383, 1928.

67. Hoff, F.: Ueber den Einfluss von Bakterienstoffen auf das Blut, Ztschr. f. d. ges. exper. Med. **67**:615, 1929. Fried and Dameshek (footnote 62).

culosis and other infections, frequently in dementia paralytica (in one case associated with convulsions they were found in large numbers) and occasionally in miscellaneous conditions, especially in the leukemias and lymphoblastomas. Other authors have described their occurrence in typhoid fever, cholera, malaria, kala-azar and other diseases.

3. It is felt that the histiocyte as seen in the peripheral blood is a distinctive cell not normally present, that it is in intimate relationship and probably the direct precursor of the monocyte, though ordinarily without relationship to the other leukocytes of the blood, and that it appears in the peripheral blood when there is unusual activity, marked irritation or leukemic proliferation of the reticulo-endothelial system.

330 Brookline Avenue.

Book Reviews

Ueber die akute und chronische gelbe Leberatrophie. Mit besonderer Berücksichtigung ihre epidemischen Auftretens in Schweden im Jahre 1927. By Prof. Dr. Hilding Bergstrand, Stockholm. Price, 14 marks. Pp. 114, with 68 illustrations and 2 colored plates. Leipzig: Georg Thieme, 1930.

In this monograph the author reports 150 cases of atrophy of the liver studied by him, 97 of which occurred during an epidemic in Sweden in 1927. The disease showed a remarkable tendency to appear at definite periods of the year, namely, spring and fall. It seemed to be epidemic, which led the author to believe that it was infectious. It was more prevalent in the cities, and more women than men were affected. Syphilis, treatment with arsphenamine and pregnancy apparently were only incidental predisposing causes.

The author draws attention to the marked clinical similarity of the course of catarrhal jaundice and that of acute yellow atrophy of the liver. It is only in the pulse rate that the two differ, the first having a bradycardia, whereas in the latter the pulse curve lies well above the temperature curve.

Results of pathologic studies conformed with the observations of other investigators. The degenerative process begins in the center of the lobule of the liver and may progress to various stages. Apparently those portions of the liver which have the greatest venous circulation are most involved. The region first attacked is that around the ligamentum falciforme hepatis. In the chronic forms, a cirrhosis results which may assume different aspects according to the character of the process. The author describes four types: (1) a large lobulated liver resembling a hepar lobatum, (2) a less coarse lobulation resembling the hobnail liver of Laennec's cirrhosis, and (3 and 4) types that display still finer irregularities of the surface.

The author also draws attention to the similarity of the course of acute yellow atrophy and that of glomerular nephritis. He suggests that in yellow atrophy the etiologic factor may be a streptococcus, the initial infection being in the upper respiratory tract. He describes a predilection of the disease for persons with a "rheumatic diathesis." Bacterial investigation of the intestinal tract of affected patients constantly showed *Streptococcus viridans,* but the disease has not been produced experimentally.

Die Procto-Sigmoskopie und ihre Bedeutung für die Diagnostik und Therapie der Krankheiten des Rektum und des Sigmoideum. By Dr. Hermann Strauss, Berlin. Second edition. Price, 17.50 marks. Pp. 96, with 68 text illustrations, 1 schematic drawing and 9 colored plates. Leipzig: Georg Thieme, 1930.

The author presents in an interesting manner the practical application of proctoscopic and sigmoidoscopic examination. In this work he has condensed the material in the first edition and has added new material.

He describes the methods of preparation of the patient and various positions for examination. His preference is the knee-chest position. A brief discussion of the anatomy of the rectum and sigmoid colon follows. The different types of instruments and their accessories are discussed and illustrated. The author prefers projected light rather than that which carries the light forward. In rare cases it is necessary to anesthetize the anus. The pathway of the tube up the bowel is described in detail. Although the author has never had the experience, perforation of the bowel has occurred and should be carefully avoided by being certain that the lumen of the bowel is ahead as the tube progresses.

Normal and pathologic observations at the various levels of the rectum and sigmoid colon are described and are beautifully illustrated in color. The indications and contraindications for proctoscopic examination are given, the chief contraindications being peritonitis, infectious processes in the area contiguous to the rectum and sigmoid, dyspneic patients and marked anemia. Finally the author discusses the use of the proctoscope in the treatment for disease by means of direct application of powders and sprays of various kinds. This procedure seems to be used quite extensively on the Continent.

This monograph is well adapted for teaching purposes and for those not entirely familiar with proctoscopic and sigmoidoscopic work.

HANDBOOK OF THERAPEUTICS. By DAVID CAMPBELL, M.D., M.A., B.Sc., "Pollok" Lecturer in Materia Medica and Pharmacology in the University of Glasgow. Price, $4.50, net. Pp. 411, with 72 illustrations. New York: William Wood & Company, 1930.

The author's introduction points out the present difficulties in teaching therapeutics when he says: "The aim of the medical curriculum is to provide the student with sufficient knowledge to treat disease rationally; yet, as a rule, there is no part of his training with which the young graduate is more dissatisfied. He is taught Pharmacology and Therapeutics before he has had the opportunity of studying disease; he may even be instructed in therapeutics by one who, though possessing a medical degree, has not himself any experience in the practice of medicine. To some extent, no doubt, this is made good in the clinique, but it is too frequently the case that when the history and physical signs have been elicited, the diagnosis, differential diagnosis, and prognosis discussed, and the pathological aspect of the disease fully considered, the all important question of treatment is either ignored or is dealt with in such a perfunctory fashion that the student carries away no clear idea of the method of treating a similar case."

The book is concise and well written, including all types of treatments used at the present time, such as hydrotherapy, diets and all biologic products. In a book of this size it is, of course, impossible to go deeply into the different subjects and at the same time cover everything. Campbell has succeeded very well for the general practitioner, and for the intern it is a book well worth having.

ABDOMINO-PELVIC DIAGNOSIS IN WOMEN. By DR. ARTHUR JOHN WALSCHEID. Price, $12.50. Pp. 1,000. St. Louis: C. V. Mosby Company, 1931.

The author presents a comprehensive volume of 1,000 pages which covers well the field of abdominopelvic diagnosis in women. The index is rather extensive and is especially valuable in a work of this kind.

The book is well illustrated and brings out many important diagnostic methods. While the author gives nothing new in the method of presenting the material or in the subject matter, it is a valuable work in that it brings together in easily accessible form up-to-date knowledge that should be of definite help, especially to those who are not working continuously in the field of gynecology. It should be of great value to the student and will serve as a convenient reference work to the practitioner.

The paper and typographic work are excellent and the illustrations are for the most part well chosen and executed.

THE EVOLUTION OF CLINICAL NOSOGRAPHY: MEDICINE IN MODERN TIMES. By KNUD FABER, M.D., LL.D., Professor of Internal Medicine, University of Copenhagen. With an Introductory Note by RUFUS COLE, M.D., Director of Hospital, Rockefeller Institute. Second edition. Price, $3.75. Pp. 222, with illustrations. New York: Paul B. Hoeber, Inc., 1930.

So few changes have been made in the text of the second edition of this interesting and stimulating book on the history of clinical description that the

reader may properly be referred to the original review (ARCH. INT. MED. **33**:532 [April] 1924). A few paragraphs have been lengthened, and a few lines withdrawn. In chapter 4, reference is made to Widal's early emphasis on the value of spinal puncture, and Widal's portrait has been added. In chapter 5 (Functional Diagnosis), new material on metabolic tests replaces two pages of the 1923 edition. Unfortunately, the index has not been changed to correspond; certain names that have been dropped from the text are still carried in the index of the second edition. The format of the book has been substantially improved. The work may again be recommended to clinicians and students for its emphasis on a comprehensive view in the clinical delineation of a disease.

THE PATHOLOGY OF INTERNAL DISEASES. By WILLIAM BOYD, M.D., M.R.C.P., Ed. Dipl. Psych., F.R.S.C., Professor of Pathology in the University of Manitoba; Pathologist to the Winnipeg General Hospital, Winnipeg, Canada. Price, $10. Pp. 837, with 298 engravings. Philadelphia: Lea & Febiger, 1931.

This volume is an important addition to the armamentarium of the student of internal medicine. It is an adjunct to the usual texts or treatises of internal medicine, but in no way supplants them. Throughout the work a correlation of pathologic anatomy, pathologic physiology and symptomatology is effected. The rationality of symptoms wherever possible is clarified by simple, logical and accurate description in excellent English. If one opens the book at any of the important chapters, one is immediately engrossed in the subject matter. There are numerous illustrations, which are excellently chosen and beautifully printed. The whole field of internal medical diseases, in contrast to those commonly considered surgical, is covered. There is, of course, some overlapping. There is a companion volume on "Surgical Pathology" by the same author.

It would be futile to attempt to describe any one chapter in detail. The chapters on the diseases of the heart, the kidneys or the thyroid, as examples, are especially well written. Sane ideas as to the classification of nephritis or of goiter are most convincingly presented. No text in the field of internal medicine that has appeared in recent years deserves more praise. It is different, readable, valuable as a reference book and in every way written from the point of view of the clinical teacher and practitioner.

MODERN METHODS OF TREATMENT. By LOGAN CLENDENING. Fourth edition. Price, $10. Pp. 819. St. Louis: C. V. Mosby Company, 1931.

This book still remains the classic in the field of medical treatment for the practitioner and student. The lucid manner in which it is written and the fact that it includes every important field in medical therapeutics make it a necessary addition to any medical library. The author has not included every new phase of therapy in this edition, but has made a selection of the subjects that are well established by careful research or are in use by the leaders in the various fields. Among those included are the administration of salyrgan, the feeding of a stomach extract in pernicious anemia, the use of Calmette's tuberculin, the treatment for undulant fever and the chemistry of the thyroid action. The chapters on dietetics and the treatment for diseases of metabolism are particularly complete.

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